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CHAPTER 1

Heterocycle-Forming Reactions of 1,2-Benzoquinones

Christopher A. Ramsden

Contents

1. INTRODUCTION

This review surveys heterocycle-forming reactions of 1,2-benzoquinones (*ortho*-quinones) **1** up to mid-2008. The main purpose of the review is to systematically analyse the modes of reaction of *ortho*-quinones **1** that lead to heterocycles and illustrate them using selected examples. We have attempted to provide comprehensive citation of the literature from 1980 to mid-2008. Some earlier papers are included but coverage of pre-1980 literature is not comprehensive. Often *ortho*-quinones are generated

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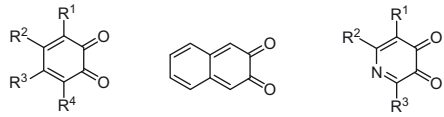
in situ by catechol oxidation and trapped without isolation and characterisation. This makes a full search of the literature difficult. However, the well-characterised examples discussed in the following sections give a representative overview of the main modes of reaction. We have not attempted to cover polycyclic or heteroquinones, for example **2** and **3**, but some examples are cited to illustrate the scope of certain reactions.

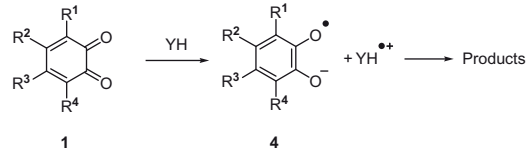


1 2 3

The 1,2-benzoquinones are often stable enough to be isolated and characterised, if necessary, but reactive enough to give products with a wide variety of reagents. This leads to a rich variety of transformations. Since they are associated with a particularly low-energy LUMO (lowest unoccupied molecular orbital), they are especially reactive towards electron-rich species. Figure 1 shows the properties of the LUMO and HOMO (highest occupied molecular orbital) of 1,2-benzoquinone calculated by the AM1 method (85JA3902).

A second general feature of *ortho*-quinone reactivity is the desire to achieve an aromatic sextet in the original carbocyclic benzoquinone ring. For these two reasons, the chemistry in this review is dominated by (i) addition and (ii) addition–elimination reactions of 1,2-benzoquinones with nucleophiles. The subdivision of the review is largely determined by the different ways in which an aromatic sextet can be achieved. However, although mechanistic aspects are emphasised in rationalising the formation of different products, some caution must be exercised in interpreting the detailed mechanisms of individual reactions. It must be born in mind that in addition to conventional nucleophilic attack, benzoquinones can also react by single-electron transfer (SET) to give a semiquinone intermediate **4** (Scheme 1), or by two-electron transfer to give a catechol dianion. In many cases any of these mechanisms can

Figure 1 The HOMO and LUMO of 1,2-benzoquinone calculated by the AM1 method.



1 4

Scheme 1

account for the same final product and little experimental evidence of mechanisms is available. Unless otherwise stated, general mechanisms in the following sections should be taken as guiding principles rather than experimental facts.

In addition to their chemical interest, some reactions of 1,2-benzoquinones are of biological significance. Dopaquinone **1** (R^1=R^3=R^4=H, R^2=$CH_2CH(NH_2)CO_2H$) is a precursor to the melanin pigments that are found widely in nature (92MI1, 04ME88, 06MI282, 07ARK23), and *ortho*-quinone formation may account for the toxic effects of some xenobiotic materials (04ME293). Examples of biologically significant heterocycle formation are emphasised wherever appropriate.

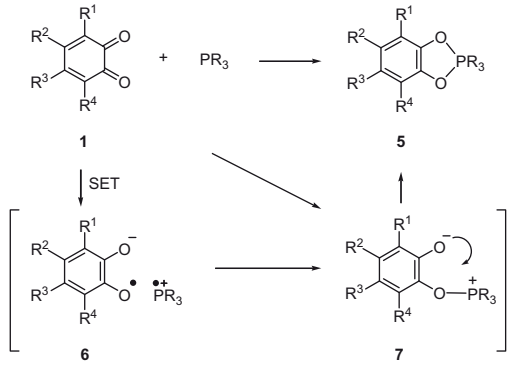
2. ADDITION REACTIONS

2.1 Intermolecular cycloadditions

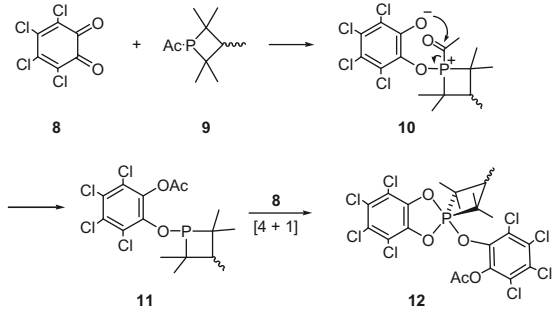
2.1.1 [4+1] Cycloadditions

2.1.1.1 Phosphorus. 1,2-Benzoquinones **1** react with a wide range of trivalent phosphorus reagents to give the [4+1] cycloadducts **5** (Scheme 2). The formation of the 1,2,5-phosphodioxole derivatives **5** is often strongly exothermic and good to excellent yields are usually obtained. Representative examples are given in Table 1.

The most plausible mechanism for these reactions is nucleophilic attack by phosphorus on oxygen to give the zwitterionic intermediates **7**. Although nucleophilic attack on electronegative oxygen is counter-intuitive, a driving force for this step is the formation of the aromatic phenolate ion, and this mode of reaction is comparable to reaction of nitro groups with trialkyl phosphites. A variation involving initial attack at carbon and C–O rearrangement to give the zwitterions **7** has been proposed based on kinetic studies (70JA4670, 83T3189, 84CJC2179). Cyclisation of the dipolar intermediates **7** can then occur giving the products **5** in a step comparable to oxyphosphetane formation in the Wittig reaction. There is some evidence that semiquinones **4** can be formed in these reactions (73JOC3423, 74REC69, 91JCS(D)19). It is possible that in some reactions SET gives a radical pair **6**, or a similar species, which then collapses to the zwitterion **7** (Scheme 2).



Scheme 2

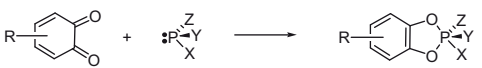


Scheme 3

Evidence for the formation of dipolar intermediates was provided when the *P*-acetylphosphetane **9** was reacted with 3,4,5,6-tetrachloro-1,2-benzoquinone (*ortho*-chloranil) **8** (75JCS(P1)1220). The product obtained was the 2:1 adduct **12**, which occurs *via* acetyl transfer in the dipolar intermediate **10** to give the phosphetane **11** (Scheme 3). A second [4+1] addition then gives the product **12**.

Because of its stability and ease of handling, many of these oxidative cyclisations of phosphorus reagents have been carried out using 3,4,5,6-tetrachloro-1,2-benzoquinone **8** (m.p. 126–129 °C). These includes reactions of diphosphanes [R_2PPR_2] (90ZNB1177), diphosphenes [RP═PR] (01HAC300), phosphines [R_3P] (75JCS(P1)1220, 80CB1406, 90AG689, 91JCS(D)19), aminophosphines [$R_2P–NR_2$] (90T2381, 90AG659), chlorophosphines [R_2PCl] (73CB2733, 91JCS(D)19), triheterophosphines [X_3P] (02RJC1764, 02HCA1364), phosphites [$(RO)_3P$] (68JOC20, 75PS73, 90JA7475, 91JGU2298, 93RJC17, 95JCS(P1)2945), chlorophosphites [$(RO)_2PCl$] (74JCS(P1)2125, 79TL193, 94T6989),

Table 1



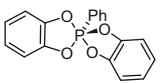
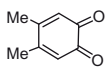
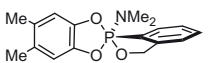
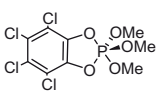
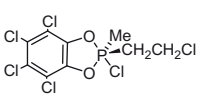
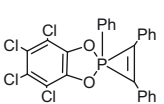
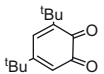
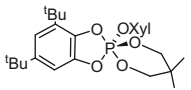
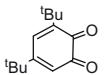
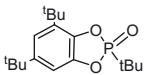
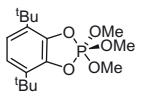
Benzoquinone	Product	Conditions	Yield (%)	m.p. (°C)	References
		Ether, room temp.	74	111	(68TL5333)
		Toluene, 0°C	72	126–129	(81JCS(P1)2239)
		Benzene, 70°C	>80	65–66	(68JOC20)
		Benzene, reflux	100	65	(73CB2733)
		Toluene, room temperature	58	143.5 (d)	(06JOC5448)

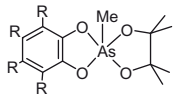
Table 1 *(Continued)*

Benzoquinone	Product	Conditions	Yield (%)	m.p. (°C)	References
		no solvent, 100 °C	75	88–90	(90JA6095)
		Benzene, 70 °C	100	85–86	(82CB901)
		CH_2Cl_2, room temperature	–	not reported	(86PS119)

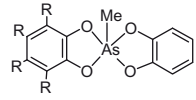
dichlorophosphites [$(RO)PCl_2$] (70JPC326), hypophosphites [$(RO)_2PR$] (68TL5333, 82JA2497), [RP═S] (86ZNB915) and a variety of phosphorus heterocycles (77TL3041, 81PS87, 82LA167, 84TL5521, 89ZNB690, 90TL3429, 90PS349, 92AG879, 92BSB359, 93PS79, 93PS219, 94CB1579, 94ZNB100, 94ZNB145, 95CB627, 04OL145, 06JOC5448).

Similar studies have been reported for the 3,5-di-*tert*-butyl derivative **1** (R^1=R^3=^{t}Bu, R^2=R^4=H) (79T1825, 80TL1449, 81PS87, 82CB901, 82PS105, 83PS283, 84CJC2179, 86PS345, 87JOM1, 90JA6095, 90JA8575, 90BSF79, 90PS349, 92PS143, 93ZNB659, 94ZNB145, 04HAC307, 07MI1737, 07MI1900), the 3,6-di-*tert*-butyl derivative **1** (R^1=R^4=tBu, R^2=R^3=H) (86ZNB915, 86PS119, 04RJC1289), the 4,5-dimethyl derivative **1** (R^1=R^4=H, R^2=R^3=Me) (81JCS(P1)2239) and the parent system **1** (R^1=R^2=R^3=R^4=H) (68TL5333).

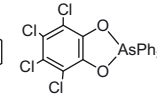
2.1.1.2 Arsenic. The derivatives **13**, **14** (73CB2738), **15**, **16** (73CB2738) and **17** (83PS129, 87JA627) have been prepared in good yield by reaction of *ortho*-quinones with the appropriate arsine derivative.



13 (R = H)
14 (R = Cl)



15 (R = H)
16 (R = Cl)



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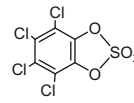
2.1.1.3 Sulphur. Irradiation of tetrachloro-1,2-benzoquinone is reported to give the sulphate **18** (53LA199). The sulphite **19** is formed in 72% yield by treatment of the di-*tert*-butyl derivative with $Ir(PiPr_3)_2(SO)Cl$ (87ZNB799).



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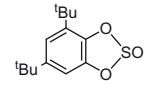

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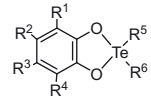
2.1.1.4 Tellurium. Derivatives of the type **20** have been prepared in good yield by reaction of *ortho*-quinones with the reagents R^5-Te-R^6 (R^5, R^6=Me, Et, Ph, Br). ESR studies of the reaction between $TeEt_2$ and 3,5-di-*tert*-butyl-1,2-benzoquinone indicate that the diradical **21**, formed *via* SET, is an intermediate in the formation of the product **20** (R^1=R^3=^{t}Bu, R^2=R^4=H, R^5=R^6=Et) (92JCS(D)2931). Formation of similar products using Ph_2Te_2 has been reported (93JOM125).



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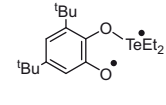

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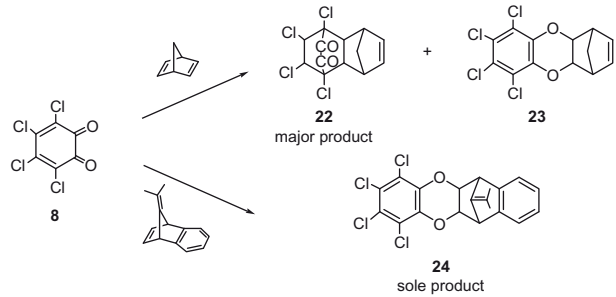
2.1.1.5 Silicon, germanium and tin. A reaction of silicon tetrafluoride with 3-*tert*-butyl-5-trityl-1,2-benzoquinone (83BAU939) and an addition using a disilane reagent (98JOM121), possibly *via* a silylene (79CC655), have been reported. The additions of tin metal and germanium(II) chloride to 3,6-di-*tert*-butyl-1,2-benzoquinone have recently been described (08MI329, 08MI251).

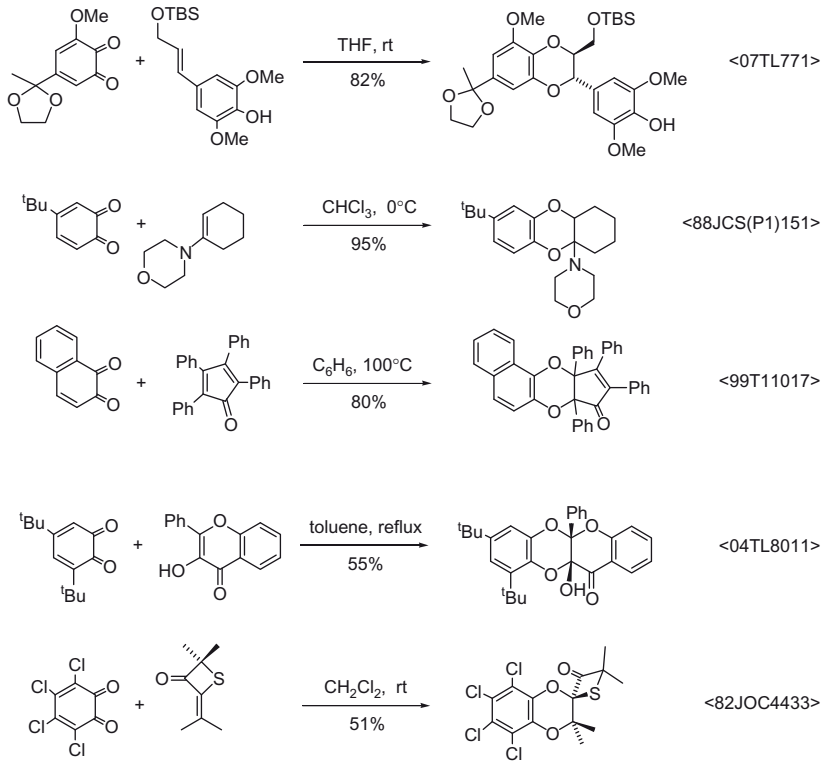
2.1.2 [4+2] Cycloadditions

Ortho-quinones can react with alkenes as either homo- or heterodienes to give formal Diels–Alder adducts. For example, *ortho*-chloranil **8** gives both cycloadducts (**22**+**23**) with norbornadiene (Scheme 4) (72TL175). However, the 2,3-dihydro-benzodioxin product, which achieves an aromatic sextet in the original quinonoid ring, is often the only product. This is the case using 7-isopropylidenebenzonorbornadiene, which gives the cycloadduct **24** (Scheme 4) (81JA565). The dihydrobenzodioxin products are commonly formed in good yield: reaction occurs with both electron-rich and -deficient dienophiles, and representative examples are shown in Scheme 5.

Early examples of [4+2] cycloadditions of 1,2-benzoquinones have been reviewed (69QR204). More recent examples giving dihydrobenzodioxins include reactions with alkenes (81JA565, 81AJC905, 82JOU1550, 83CB2554, 00AJC109), styrenes (79JOC2518, 87H969, 03CL420, 06EJO335, 07TL771), fulvenes (76T147, 95CL383, 95TL1605, 96T4029), dienes (83H197, 83H1017, 88JOC3073), cyclobutadienes (85JOC3839), enones (80IJB301, 82JOC4429, 82ACB613, 85S619, 91SA893, 99T11017, 02HCA1295), enediones (81JOC2021, 96JOC6656), heteroalkenes (C═X) (83T3189, 83PS27, 83PS47, 85ZNB1077, 00T6259), ketenes and ketinimines (51LA17, 80LA1836, 81ZNB609, 85RTC37, 07C240), enamines (65LA187, 88JCS(P1)151, 96JOC5581, 07TL1605), polyhetero-substituted alkenes (79CC606, 03JA16206) and heterocycles (72JCS(P1)532, 77TL3115, 82H1197, 83TL3745, 83TL5481, 84TL2993, 84JHC1841, 86TL3915, 86RTC403,



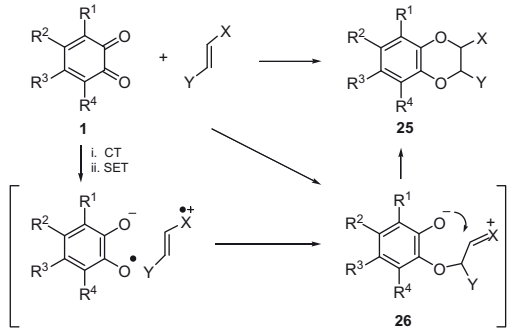
Scheme 4



Scheme 5

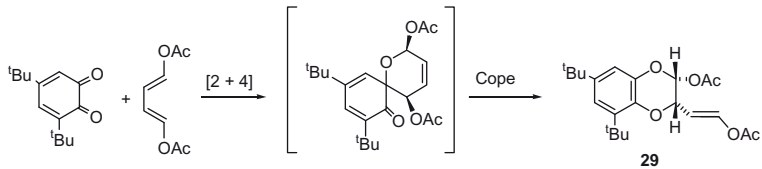
87H969, 87JRM0253, 89JCS(P1)1147, 91JRM3139, 96RJC358, 96SC217, 96T6725, 03H265, 04TL8011).

Like the oxidative cyclisations discussed in Section 2.1.1, these formal Diels–Alder cycloadditions (e.g. Scheme 5) are probably not pericyclic reactions. Tedder and co-workers (69JCS(C)1694, 72JCS(P1)532) have suggested that reaction of *ortho*-quinones with furans occurs *via* dipolar intermediates of the general type **26** (Scheme 6), and this type of intermediate has been proposed by other workers (83T3189, 88JCS(P1)151). Studies of solvent effects on the rate of reaction suggest a multistep reaction mechanism (88JCS(P1)151, 90T7951) and there is evidence of initial formation of charge transfer (CT) complexes (84JHC1841, 88JCS(P1)151). Formation of the dipolar intermediate may be preceded by SET: reaction of tetrathiafulvalene with *ortho*-chloranil is reported to give a mixture of the radical ion pair **27** and the dihydrobenzodioxin **28** (03JA16206).



1 25 26

Scheme 6



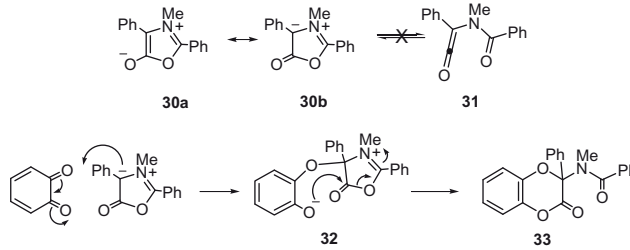
29

Scheme 7

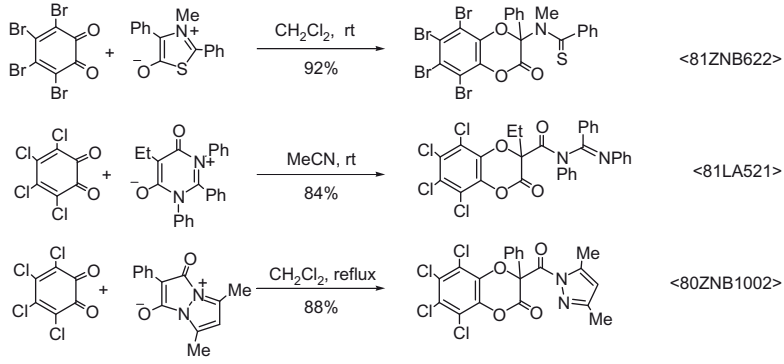
27 28

A full discussion of the mechanistic aspects of these reactions is beyond the scope of this review. Caution must be exercised in proposing mechanistic pathways in the absence of firm experimental evidence. For example, reaction of 1,3-dienes gives [4+2] cycloadducts (e.g. **29**) but these may well occur *via* a [2+4] addition to give an initial adduct followed by a Cope rearrangement (Scheme 7) (94CC1341, 96JCS(P1)443).

Some dipolar heterocycles undergo cycloadditions with *ortho*-quinones to give products that are formally [4+2] cycloadducts of an acyclic ketene tautomer. For example, the mesoionic 1,3-oxazolium-5-olate **30** reacts with 1,2-benzoquinone to give the cycloadduct **33** (Scheme 8) (81ZNB622). It is well established that these heterocycles, for example **30**, do not equilibrate with their acyclic tautomers, for example **31** (76AHC1, 80AHC1, 80LA1836, 85CB2079). A more plausible mechanism for the formation of the adduct **33**, and related products, involves reaction of the 1,3-dipole as a C-nucleophile to give the zwitterionic intermediate **32**, which then cyclises with ring cleavage



Scheme 8



Scheme 9

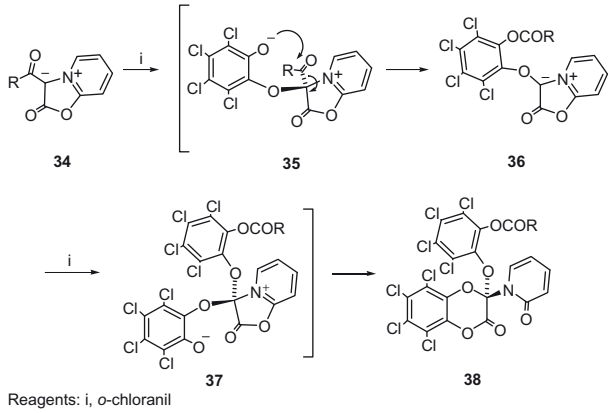
(Scheme 8) (81ZNB622). See Section 2.1.4 for mention of an alternative mode of reaction, which may compete with [4+2] cycloaddition for some 1,3-oxazolium-5-olates (80LA1836).

Further examples of this type of reaction by 1,3- and 1,4-dipolar heterocycles are shown in Scheme 9, and other examples have been described (80ZNB1002, 81LA521, 81ZNB609, 81ZNB622, 83H1271, 85CB2079). Some closely related dipolar heterocycles react *via* alternative pathways leading to [4+3] and [4+4] cycloadducts, which are described in Sections 2.1.3 and 2.1.4.

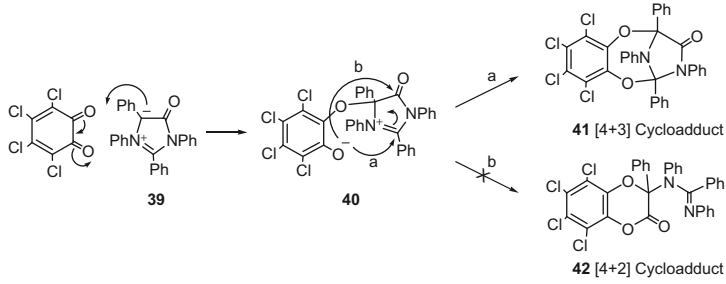
Evidence in support of zwitterionic intermediates is provided by the reaction of the *C*-acyl 1,3-dipoles **34** (R=Me, Ph) with *o*-chloranil (Scheme 10) (80LA1836). The initial intermediate **35** undergoes acyl transfer to give a new mesoionic derivative **36**, which reacts with a second molecule of *o*-chloranil, *via* a new zwitterion **37**, to give the final adduct **38**.

2.1.3 [4+3] Cycloadditions

It is interesting to note that some type A mesoionic heterocycles (e.g. **30**) give [4+2] cycloadducts (Schemes 8 and 9) (Section 2.1.2) whereas other



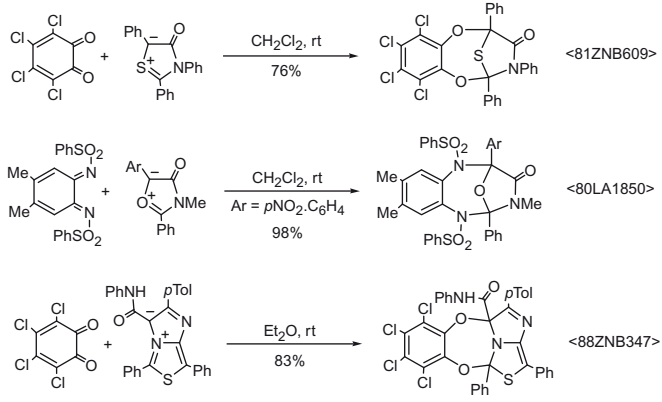
Scheme 10



Scheme 11

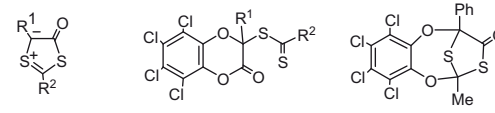
type A mesoionic compounds give [4+3] cycloadducts. For example, the 1,3-diazolium-4-olate **39** gives the [4+3] cycloadduct **41** and not the [4+2] cycloadduct **42** (Scheme 11) (80LA1850). Both these types of product can be regarded as potentially arising by alternative cyclisations of a common zwitterionic intermediate **40** (80LA1850). In this case, cyclisation onto the 1,3-dipolar fragment (pathway a, Scheme 11) gives the [4+3] product, and cyclisation onto the carbonyl group (pathway b) leading to a [4+2] product is not observed. In this review we describe products of the type **41** as [4+3] cycloadducts because they are the result of the reaction between a heterodiene and a 1,3-dipole; in some papers they are described as [4+4] adducts (88ZNB347).

Typical examples of this type of [4+3] cycloaddition with 1,3-dipolar heterocycles are shown in Scheme 12, and further examples can be found in the papers cited in this section (80LA1850, 81ZNB609, 81ZNB622, 88ZNB347).



Scheme 12

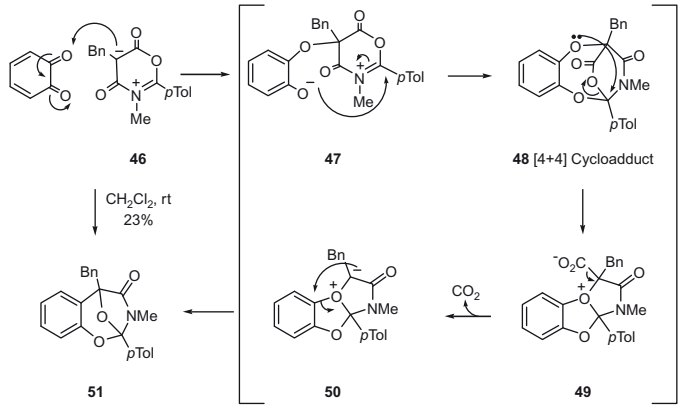
The mesoionic dithiolylium-4-olates **43** provide examples of both types of cycloadduct. All but one of the derivatives studied react with *o*-chloranil to give the [4+2] cycloadducts **44** (14–96% yield); the exception is the 2-methyl-5-phenyl derivative **43** (R^1=Ph, R^2=Me), which gives the [4+3] cycloadduct **45** (59% yield) (81ZNB609).



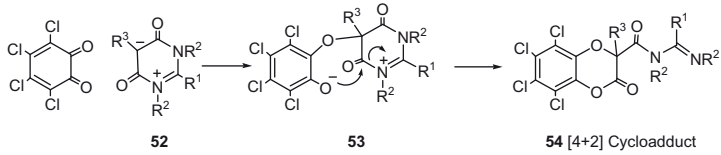
43 **44** **45**

2.1.4 [4+4] Cycloadditions

The [4+4] cycloadditions discussed in this section are analogous to the [4+3] cycloadditions discussed in Section 2.1.3 except that (i) the reactants are cross-conjugated mesomeric betaines (80AHC1, 85T2239), which therefore react as 1,4-dipoles rather than as 1,3-dipoles and (ii) the initial [4+4] cycloadduct undergoes elimination of carbon dioxide and rearrangement. A typical example is shown in Scheme 13 in which the oxazinium-olate **46** reacts with *ortho*-quinone to give the product **51** (79TL237, 82ZNB222). A number of other examples using *o*-chloranil have been described. The early stages of the suggested mechanism (Scheme 13), which involves the intermediate **47**, are analogous to those for the formation of [4+3] cycloadducts by 1,3-dipolar heterocycles (Scheme 11, pathway a). In the case of these [4+4] cycloadducts, for example **48**, elimination of carbon dioxide readily occurs leading *via* the postulated intermediates **49** and **50** to the product **51**. There is evidence that when carbon dioxide can be eliminated some mesoionic heterocycles



Scheme 13



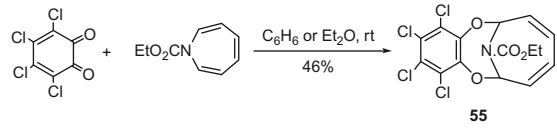
Scheme 14

(e.g. 1,3-oxazolium-5-olates (münchnones)) undergo a similar elimination-rearrangement sequence in competition with [4+2] cycloaddition (80LA1836).

In contrast to the oxazinium-olates, for example **46**, the isoelectronic diazinium-olates **52**, which cannot eliminate carbon dioxide, undergo the alternative cyclisation of the zwitterionic intermediate **53** resulting in formation of a [4+2] cycloadduct **54** (Scheme 14) (see also Section 2.1.2, Scheme 9) (81LA521).

2.1.5 [4+6] Cycloadditions

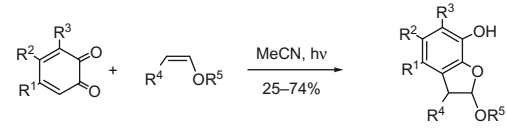
Reaction of *o*-chloranil with 1-ethoxycarbonyl-1*H*-azepine at room temperature (70 min) gives the [4+6] cycloadduct **55** as the major product (equation (1)). Two isomeric [4+2] adducts were also formed in yields of 15% and 7% (82H1197).



(1)

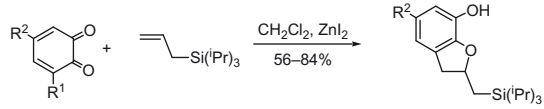
2.1.6 [3+2] Cycloadditions

The regioselective formation of the [3+2] photocycloadducts **56** has been reported to occur in moderate to good yield when 1,2-benzoquinones are irradiated with vinyl ethers in acetonitrile solution (equation (2)) (96CC703). In benzene solution the [4+2] cycloadduct is also formed, sometimes as the major product.



56 (2)

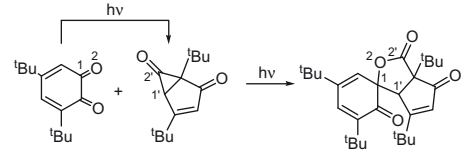
A thermal, Lewis acid-catalysed [3+2] cycloaddition of allylsilanes giving the dihydrobenzofurans **57** has also been described (equation (3)) (02TL5349). The mechanism has been interpreted in terms of formation of a β-silyl cation by a zinc–benzoquinone complex, followed by cyclisation, and elimination of isobutene when R^1=^{t}Bu.



R^1, R^2 = H or ^{t}Bu

57 (3)

2.1.7 [2+2] Cycloadditions



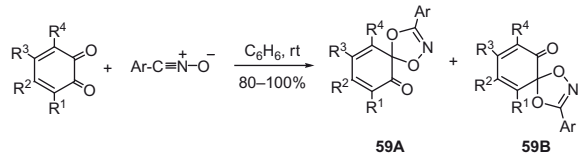
58 (4)

Irradiation of 3,5-di-*tert*-butyl-1,2-benzoquinone gives the tricyclic furan derivative **58** in 10% yield (06RJO227, 07RJC1055). The formation of this product has been interpreted in terms of initial photoisomerisation followed by addition of the cyclopropanone ring to the least-hindered carbonyl group (equation (4)) (08T9784). Tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptan-3-one also gives [2+2] adducts (83H1017).

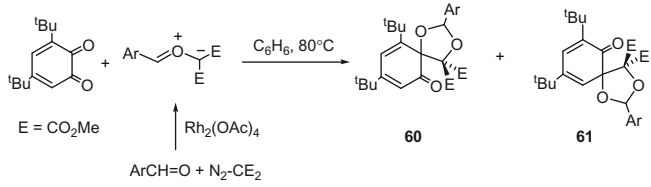
2.1.8 [2+3] Cycloadditions

In contrast to heterocyclic 1,3-dipoles (Sections 2.1.3–2.1.5), which react with the heterodiene fragment, acyclic 1,3-dipoles react with discrete carbonyl groups of benzoquinones to give [2+3] 1,3-dipolar cycloadducts. For example, nitrile oxides and di- or trisubstituted benzoquinones give a

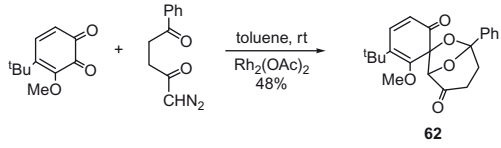
mixture of the regioisomers **59A** and **59B**, when the benzoquinone is unsymmetrical (equation (5)) (96TL5623, 99T14199). Monosubstituted benzoquinones tend to give *bis* adducts.



(5)



Scheme 15

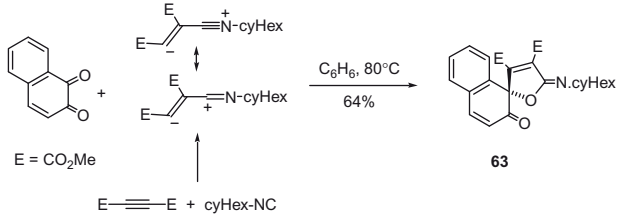


(6)

For a discussion of reactions with diazoalkanes, including diazomethane, see Section 3.1.3.1.

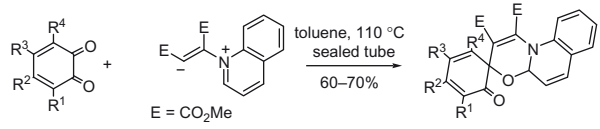
Reaction with carbonyl ylides, generated by *in situ* Rh(II) catalysed decomposition of diazomalonates in the presence of an aromatic aldehyde, gives mixtures of regioisomeric spiro[1,3]dioxolanes, for example **60** and **61** (Scheme 15), in moderate to good yields (40–74%). The ratio of regioisomers depends on the quinone ring substituents (03TL8407, 05T2849). By employing bifunctional diazoketones this approach has been used to prepare a number of spiro-oxabicycles, for example **62** (equation (6)) (98TL5627, 02T4171).

Reaction between dimethyl acetylenedicarboxylate (DMAD) and cyclohexyl isocyanide results in *in situ* generation of a dipolar species, which gives 1,3-adducts with carbonyl groups. An illustrative example is given in Scheme 16, and here it is interesting to note that in naphtha-1,2-quinone only the benzoyl carbonyl group reacts, resulting in exclusive formation of the cycloadduct **63** (Scheme 16) (03T10279). Related additions giving γ-spirolactones have been observed using DMAD and triphenylphosphine (97JCS(P1)3129, 00S1713).



Scheme 16

2.1.9 [2+4] Cycloadditions



(7)

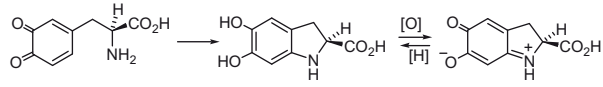
Reaction of several 1,2-benzoquinones with quinoline and DMAD has been shown to result in formation of 1,4-dipolar cycloadducts in good yield as shown in equation (7) (08T3567). For another possible example of [2+4] cycloaddition see Scheme 7 (Section 2.1.2).

2.2 Intramolecular additions

2.2.1 Five-membered ring formation

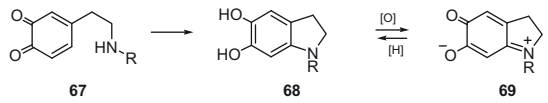
The most important example of intramolecular addition to an *ortho*-quinone is the spontaneous cyclisation of dopaquinone **64** to give L-cyclodopa **65**, which is an intermediate in the biosynthesis of melanin pigments (Scheme 17) (92MI1, 04ME88, 06MI354). Under oxidative conditions the dihydroindole **65** is rapidly oxidised to dopachrome **66**. A number of other examples of the facile cyclisation of 2-aminoethyl derivatives of *ortho*-quinones have been described (80JOC2899, 83JOC562, 94JMC1084, 95JCS(P2)259, 97JCS(D)2813, 98JCS(D)1315, 01JA9606, 02AC5047), and the formation of 2,3-dihydro-5,6-dihydroxyindoles in this way was reviewed in 2005 (05AHC(89)1).

Secondary amines (e.g. **67**) also cyclise to the corresponding dihydroindoles (e.g. **68**) (78JMC548, 91PHA426, 93PHA273, 93JCS(P2) 2435, 03PCR397), which are usually further oxidised to 'aminochromes' **69** (Scheme 18) (65AHC205, 93JCS(F)803, 05AHC(89)1).



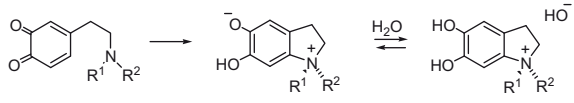
64 **65** **66**

Scheme 17



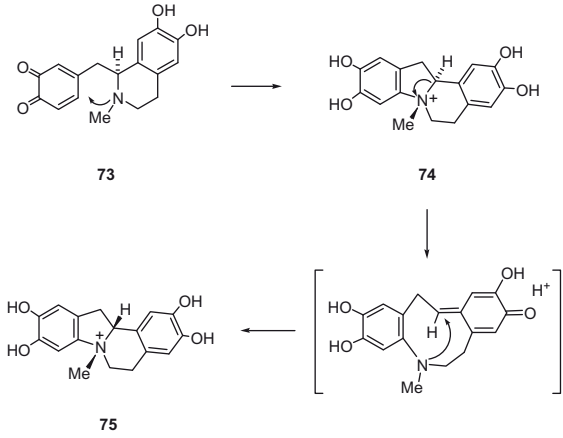
67 68 69

Scheme 18



70 71 72

Scheme 19



73 74 75

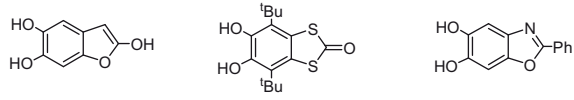
Scheme 20

Tertiary amines **70** cyclise to give the betaines **71**, which in aqueous media protonate to give the salts **72** (Scheme 19) (97JBC26226, 00JCS(P1) 4306). The earliest example of a tertiary amine cyclisation was described by Robinson (32JCS789) and Schöpf (32LA22) who showed that the *ortho*-quinone **73**, formed from laudanosoline, cyclised to give a product assumed to have the *trans* structure **74**. More recent work by Meyer and co-workers on the asymmetric synthesis of related natural products has shown that the initial *trans*-product **74** rearranges to the thermodynamically more stable *cis*-product **75**, *via* an intermediate quinomethane (Scheme 20) (91JA2789, 92JA8483).

The rates of cyclisation of a wide range of *ortho*-quinone amines have been studied using pulse radiolysis (01JPPB123) and cyclic voltammetry (83JOC562). The rates of cyclisation of amines increase in the order primary < secondary < tertiary: the influence of amine substituents and chain length on the rates and modes of intramolecular cyclisation was comprehensively reviewed in 2007 (07ARK23). It is interesting to note

that intramolecular cyclisation always occurs at position 5, and not at position 3, of the *ortho*-quinone ring (e.g. Schemes 17–19). A quantum mechanical study has concluded that this regioselectivity is mainly due to the difference in the electronic energies of the conjugated systems in the two transition states (06T4884).

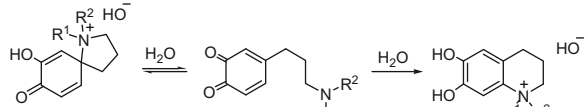
In addition to amines, other *ortho*-quinone sidechains have been reported to undergo intramolecular cyclisation to form five-membered heterocyclic rings. These include acetic acids giving benzofurans, for example **76** (99ABB98), dithiocarbonic esters giving benzo[1,3]dithiolones, for example **77** (06MI708), and benzamides giving benzoxazoles, for example **78** (59JA6222). Also, some propylamine derivatives form transient five-membered spiroheterocycles (see Section 2.2.2).



76 **77** **78**

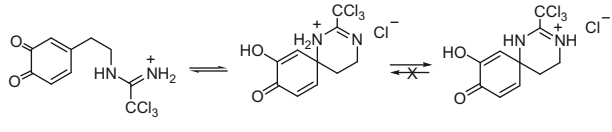
2.2.2 Six-membered ring formation

Secondary and tertiary 3-aminopropyl derivatives **80** (R^1=alkyl, R^2=H or alkyl) cyclise to give the bicyclic derivatives **81** (00JCS(P1) 4306, 03PCR397, 03ACR300). The diethyl derivative **81** (R^1=R^2=Et) has been isolated and characterised (00JCS(P1)4306). Pulse radiolysis studies have shown that rapid transient formation of the spiro derivatives **79** occurs but these kinetic products rapidly decay to the thermodynamic products **81** (Scheme 21) (07ARK23). An interesting exception is the formation of the stable spiro derivative **83** by the amidine **82**. It is assumed that the initial cyclisation product irreversibly tautomerises to the stable product **83** (Scheme 22) (05OBC2387, 06PCR170, 09OBC944).



79 **80** **81**

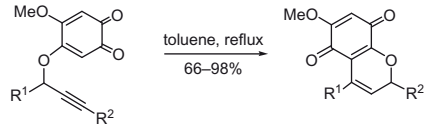
Scheme 21



82 **83**

Scheme 22

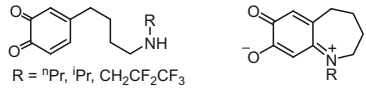
Propargyl derivatives, for example **84**, undergo Claisen rearrangement and cyclisation to give 2*H*-1-benzopyran-5,8-quinones (equation (8)) (87S790, 90JCS(P1)2979).



84 (8)

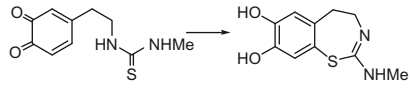
2.2.3 Seven-membered ring formation

The derivatives **86** were isolated as purple solids in moderate yield (50–60%) when the *ortho*-quinones **85** were generated under oxidative conditions. It should be noted that the corresponding tertiary amines rearrange to the tautomeric *para*-quinomethanes, which cyclise forming pyrrolidinium salts (03OBC3120).



85 **86**

When the thiourea **87** was formed from the corresponding catechol, it cleanly cyclised to the seven-membered heterocycle **88** (equation (9)) (05OBC2387, 06PCR170, 09OBC944).

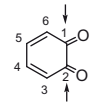


87 **88** (9)

3. ADDITION–ELIMINATION REACTIONS

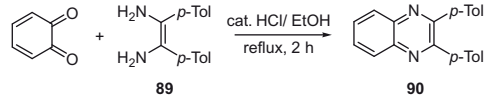
3.1 Intermolecular addition–elimination

3.1.1 Reaction at C1 and C2

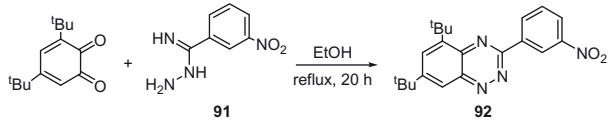


The reaction of 1,2-benzoquinones with 1,2-diamines gives pyrazine derivatives, but examples since 1980 are very limited. For example, reaction of the diamine **89** with 1,2-benzoquinone gives the 2,3-di-*p*-tolylquinoxaline **90** (equation (10)) (85JA1501). In a similar way, a

reaction with ethylenediamine gave a mixture of a 6,7-di(morpholin-4-yl) quinoxaline (42%) and the corresponding 1,2,3,4-tetrahydroquinoxaline (86CHE771). When 3,5-di-*t*-butylbenzoquinone was reacted with the benzimidic hydrazide **91**, the 1,2,4-benzotriazine **92** was obtained (59%) (equation (11)) (82JHC1201).

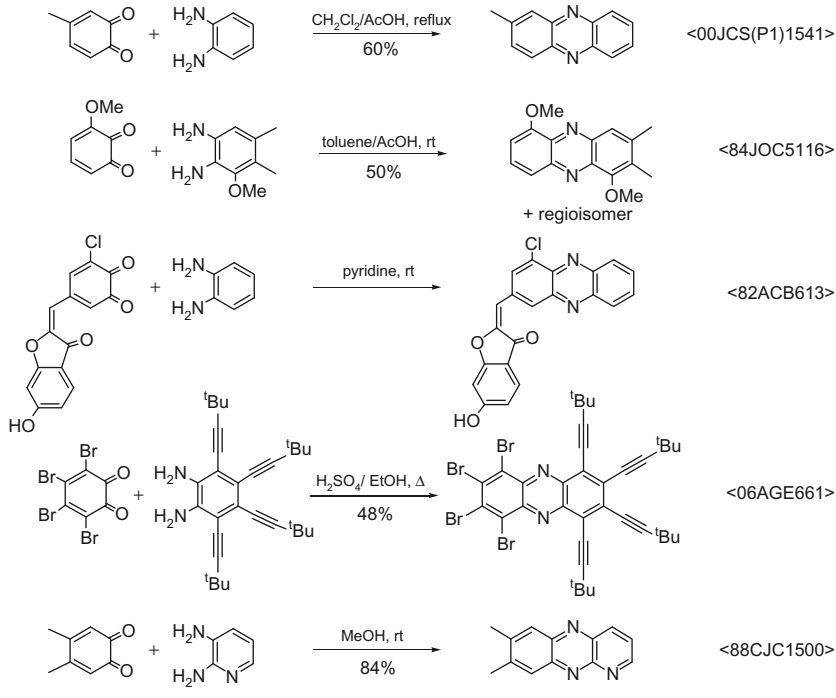


(10)



(11)

The most common application of this mode of reaction of 1,2-benzoquinones is condensation with 1,2-diaminobenzenes to form phenazines: illustrative examples are shown in Scheme 23. A number of other phenazine derivatives have been made in this way (09CB2922, 13CB3011, 25HCA218, 27HCA64, 28JCS353, 34JA477, 35HCA362, 37MI218, 38MI160,

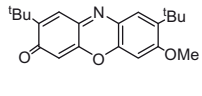


Scheme 23

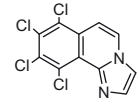
46JA2246, 55CB802, 55RTC937, 55LA1, 55ZOB2161, 58JCS859, 67MI53, 76BCJ2333, 82ACB613, 83MCL149, 84JOC5116, 98JFA111, 98T14791, 00JCS(P1)1541, 02JCS(P2)1553, 03EJM899, 06AGE661). Similar reactions of naphthoquinones have been reported (54JCS2895, 85JA1501, 96CHE577). 3,3,6,6-Tetrachloro-2,2-dihydroxycyclohexanone has been used as a 1,2-benzoquinone equivalent to prepare 4-chloro-1-hydroxyphenazines (07TL9137).

Use of 2,3- or 3,4-diaminopyridine gives pyrido[2,3-*b*]quinoxalines or pyrido[3,4-*b*]quinoxalines, respectively, and one example is included in Scheme 23 (88CJC1500).

In addition to 1,2-diamines, there are a limited number of studies describing this mode of reaction of *ortho*-quinones with other dinucleophiles. Reactions with 2-aminophenol and 2-aminothiophenol derivatives give phenoxazin-3-ones and phenothiazin-3-ones, for example **93** (25HCA218, 69LA106, 72JCS(P1)813). Reaction of tetrachloro-1,2-benzoquinone with 1-vinyl-1*H*-imidazole has been reported to give the tricyclic product **94** in 75% yield (05ZNB106), and reaction with P_4S_{10} gives a heptachlorodibenzothiophene (3.3%) (02PS2725).

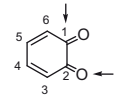


93



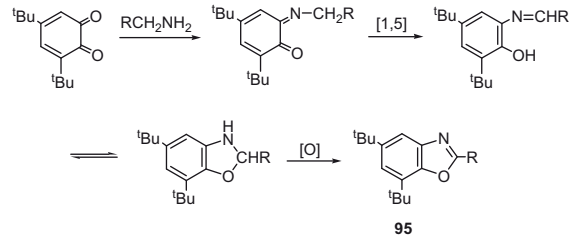
94

3.1.2 Reaction at C1 and O2



3.1.2.1 Five-membered ring formation. While investigating methods of oxidising primary amines to ketones, Corey and Achiwa showed that 3,5-di-*t*-butyl-1,2-benzoquinone and amines of the type RCH_2NH_2 give benzoxazoles (69JA1429). In this way, benzylamine gave the benzoxazole **95** (R=Ph) in 73% yield. The *t*-butyl substituents are necessary to prevent Michael addition. These reactions involve Schiff base formation, rearrangement to give a phenol and oxidative cyclisation as shown in Scheme 24. Recent examples include the use of (i) 2-aminoethanol (94CCC227), (ii) (aminomethyl)trimethylsilane ($H_2NCH_2SiMe_3$) to give the unsubstituted derivative **95** (R=H) (92JOC6687) and (iii) 1-amino-3-butyne (homopropargylamine) to give an allene derivative **95** (R=CH=C=CH_2) (04JA8038).

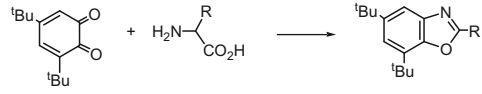
A similar transformation, this time involving a decarboxylation step, occurs with α-amino acids (equation (12)), but it should be noted that complex mixtures were obtained using other, less-hindered, quinones



95

Scheme 24

(78JOC509). A number of amino acids and dipeptides have been used in this way to prepare 5,7-di-*t*-butylbenzoxazoles **95** for antibacterial evaluation (94CCC227, 05MOL783, 06BMC5850). Other amino acid derivatives (00TL8773) and also benzamidine (88JCS(P1)2169) have been reported to give benzoxazoles with 3,5-di-*t*-butyl-1,2-benzoquinone.



95 (12)

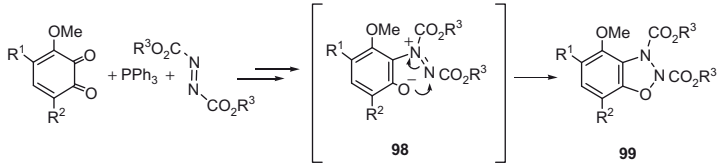
3,5-Di-*t*-butyl-1,2-benzoquinone reacts with phosphorus ylides to give benzo[*b*]furan derivatives (e.g. **96** (19%) and **97** (60%)) (80CB2950, 92JCS(P1)283, 03JHC399) by mechanisms having similarities to that shown in Scheme 24.

96 97

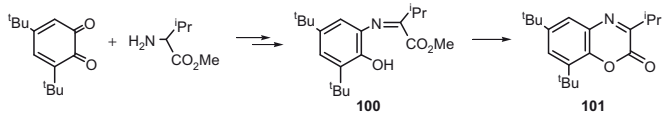
Reaction of 4,6-disubstituted-3-methoxy-1,2-benzoquinones with dialkyl azodicarboxylates and triphenylphosphine gives dihydro-1,2,3-benzoxadiazoles **99** in good yield (64–94%) (Scheme 25). A multistep mechanism leading to the zwitterionic intermediates **98**, which then cyclise to the products **99**, has been proposed (05OL5139). An *N*,*N*-diphenyl-2,3-dihydro-1,2,3-benzoxadiazole has been obtained (40% yield) by reaction of 3,5-di-*t*-butyl-1,2-benzoquinone with *N*-phenyliminophosphorane ($PhN^{-}—^{+}PPh_3$) (see also Section 3.1.3.2) (02SC2779).

Ortho-chloranil **8** and diethylphosphorylmethyl methyl sulphoxide [$(EtO)_2PO.CH_2SO.Me$] (2 equiv.) give a tetrachloro-2,3-dihydrobenzofuran derivative (55%) (98SC3579).

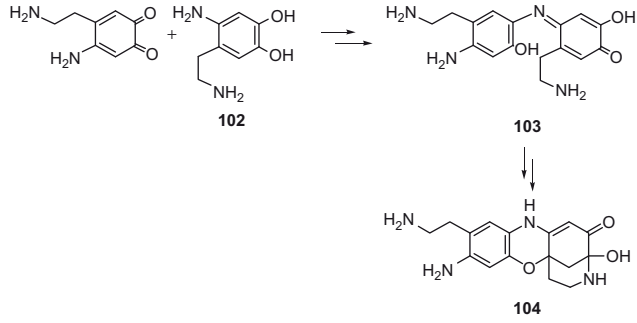
3.1.2.2 Six-membered ring formation. Reactions of *ortho*-quinones with 1-(dimethylamino)-but-3-ene-1-yne (80MI29) and ethyl diethoxyphosphorylacetate (92PS241) have been reported to give benzo[*b*]pyran derivatives.



Scheme 25



Scheme 26



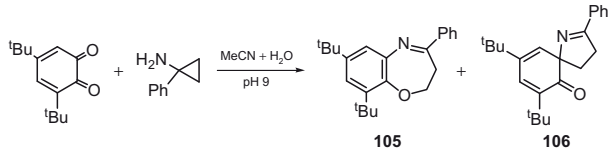
Scheme 27

Several reports of *ortho*-quinones giving benzo[*b*]-1,4-oxazine derivatives have appeared (71T1831, 92T8515, 99HCA1502, 00TL8773). For example, reaction with the methyl ester of valine gives the benzoxazol-2-one **101** in 53% yield (00TL8773). In contrast to the reactions of amino acids (equation (12)), decarboxylation cannot occur with the esters: the expected phenol tautomer **100** therefore forms and, in this case, preferentially cyclises to the six-membered product **101** (Scheme 26). Similar behaviour has been observed using the ethyl ester of glycine (71T1831).

Oxidation of the neurotoxin 6-aminodopamine **102** at concentrations higher than 5×10^{-3} M leads to formation of the tetrahydrophenoxazine derivative **104** (38%) (92T8515). A mechanism involving intermediate formation of the quinone imine **103** followed by 6-*exo*-*trig* cyclisation has been proposed (Scheme 27).

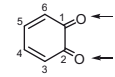
3.1.2.3 Seven-membered ring formation. Reaction of 3,5-di-*t*-butyl-1,2-benzoquinone with 1-phenylcyclopropylamine gives a mixture of the

dihydrobenzoxazepine **105** and the spirocyclic product **106** (equation (13)) (91JOC1353).



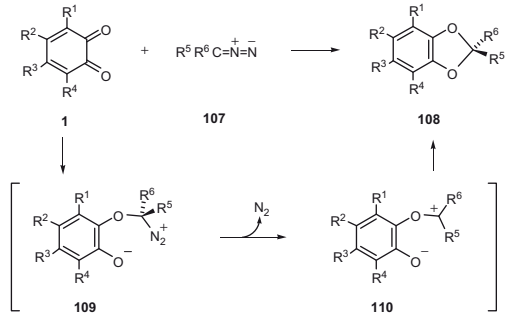
(13)

3.1.3 Reaction at O1 and O2



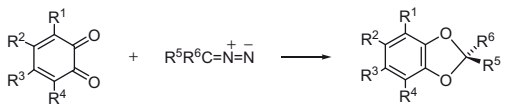
3.1.3.1 Nitrogen elimination. 1,2-Benzoquinones react smoothly with diazoalkanes **107**, including diazomethane, to give benzo[1,3]dioxoles **108**, usually in good yield (Scheme 28). Selected examples are shown in Table 2. Other examples have been described (71CB78, 80IJB975, 81PHA805, 85TL5317), and additional examples can be found in the papers cited in Table 2. Under some conditions, diazomethane also gives an indazole by cycloaddition to the 3,4 C═C bond (81MI1944) and an epoxide by cycloaddition to a C═O bond (04H23).

These reactions can best be regarded as occurring *via* the betaines **109**, formed by nucleophilic addition of the diazoalkane, followed by loss of nitrogen and cyclisation of the intermediates **110**. There is no experimental evidence to suggest that formation of a [2+3] cycloadduct precedes formation of acyclic adducts such as **109**, or that the adducts **109** cyclise to give [2+3] cycloadducts. Evidence supporting the formation of the intermediates **110** has been provided by the reaction of *ortho*-chloranil with three equivalents of 1-phenyldiazoethane (Scheme 29) (85TL5317). In addition to the major product **111** (81%), there was a 19% yield of the ether **112**, which can be rationalised by proton transfer in the dipolar intermediate (Scheme 29).

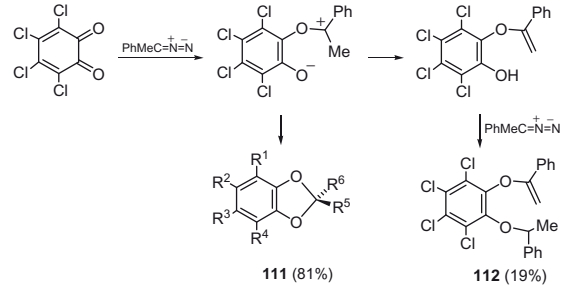


Scheme 28

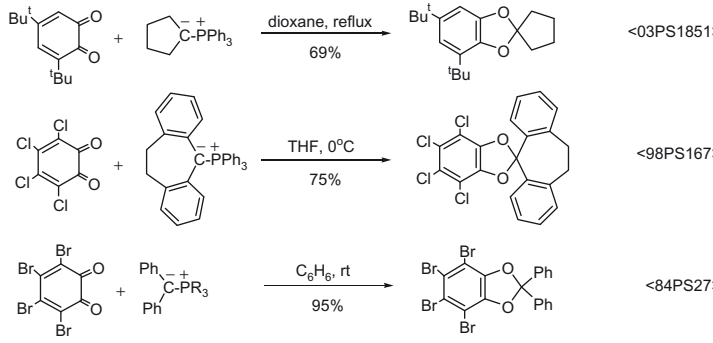
Table 2



R^1	R^2	R^3	R^4	R^5 R^6	Conditions	Yield (%)	m.p. (°C)	References
H	CPh_3	H	H	Ph Ph	Ether, rt	76	258–259	(35JA1479)
Cl	Cl	Cl	Cl	H H	Ether, rt	>80	171	(51JCS1368)
Cl	Cl	Cl	Cl	Ph Ph	C_6H_6, rt	>80	141	(51JCS1368)
Cl	Cl	Cl	Cl	Ph Ph	Pet. ether, rt	–	143	(51LA30)
H	CPh_3	H	Br	Fluoren-9-yl	C_6H_6, warm	70	262	(52JCS446)
H	Me	Me	H	H H	Ether, rt	6	43–47	(55LA1)
H	Me	Me	H	Fluoren-9-yl	Ether, rt	34	180	(55LA1)
H	CPh_3	H	H	Xanthen-9-yl	Ether, rt	60	264	(59CJC863)
Cl	Cl	Cl	Cl		CH_2Cl_2, rt	73	240	(80JOC4337)
^{t}Bu	H	H	^{t}Bu	H H	Ether, rt	55	41–42	(81MI1944)
Cl	Cl	Cl	Cl	4-Chloro-xanthen-9-yl	Ether, rt	–	255	(84LA196)



Scheme 29

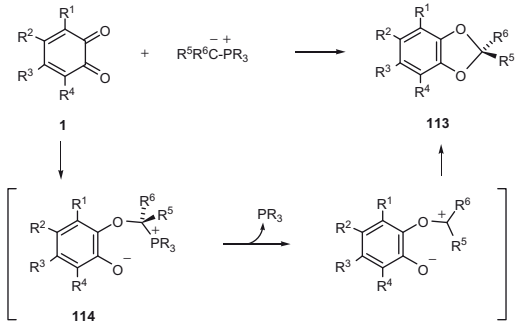


Scheme 30

In a study using a bicyclobutane derivative, Hogeveen and co-workers showed that no skeletal rearrangement occurred and concluded that a carbene was not an intermediate in this reaction (80JOC4337).

3.1.3.2 Phosphine (PR_3) elimination. As a general rule, phosphorus ylides react with 1,2-benzoquinones to give 1,3-benzodioxoles **113** with elimination of a phosphine (69TL2101, 83JRM0658, 83MI402, 84PS27, 86JCS(P1)415, 92PS285, 98PS167, 01JCS(P1)3073, 03PS1851). Wittig products, formed with elimination of the phosphine oxide, are not usually observed: the pathway leading to an aromatic sextet appears to be favoured over forming a strong phosphorus–oxygen bond. Representative examples are given in Scheme 30. This mode of reaction contrasts with the behaviour of polycyclic 1,2-quinones, such as phenanthrene-9,10-quinone, where the Wittig product usually forms and reacts further to give benzofuran- and benzopyran-type products (69TL457, 85JCS(P1)429, 89JCS(P1)2329, 90JCS(P1)2127, 92JCS(P1)283, 94JCS(P1)2107).

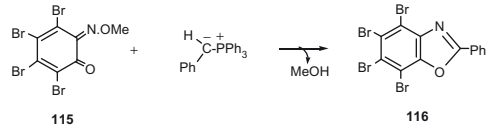
The formation of the products **113** can be envisioned as occurring *via* the betaines **114**, which cyclise by either an S_N1 (as shown) or S_N2



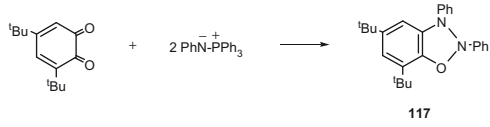
Scheme 31

mechanism (Scheme 31). Variations on this mechanism have been proposed (84PS27, 92PS285, 03PS1851), and it is possible that the betaines **114** are formed by initial SET followed by radical coupling. In some cases betaine products have been isolated (93T8691, 01JCS(P1)3073).

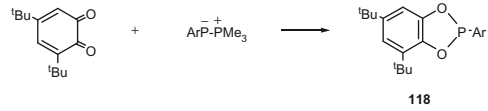
Three variations of this methodology lead to different heterocyclic products. Use of the mono-oxime **115** results in formation of the benzoxazole **116** after elimination of methanol (equation (14)) (89T4585). Use of two moles of *N*-phenyliminophosphorane (PhN^{-}–$^{+}PPh_3$) gives the 2,3-dihydro-1,2,3-benzoxadiazole **117** (40%) (equation (15)), presumably after initial formation of the quinone imine (02SC2779). Reaction with phosphanylidene phosphoranes (ArP^{-}–$^{+}PMe_3$) gives 1,3,2-benzodioxophospholanes **118** (equation (16)) (04CC146).



(14)

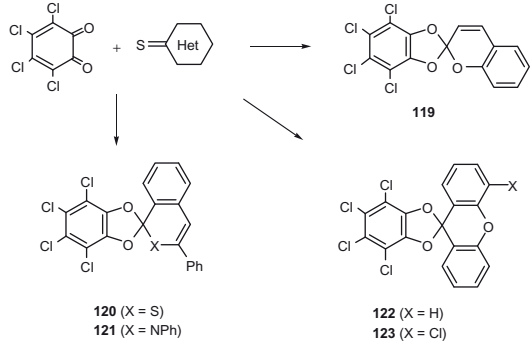


(15)

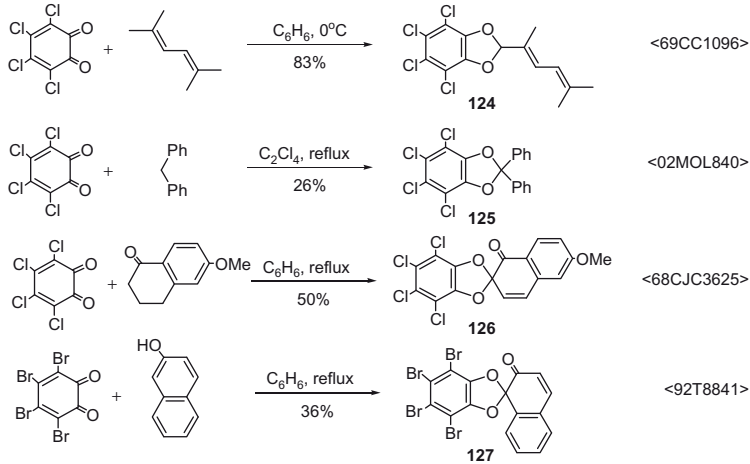


(16)

3.1.3.3 Sulphur elimination. A number of examples of 3,4,5,6-tetrachloro- (and tetrabromo-) 1,2-benzoquinones reacting with heterocyclic thiones to give spirocyclic benzo[1,3]dioxoles, as shown in Scheme 32, have been reported. In particular, coumarin-2-thione gave **119** (59CJC863), 2-phenylbenzo[*d*][1,3]thiazine-4-thione gave **120** (74TL1355),



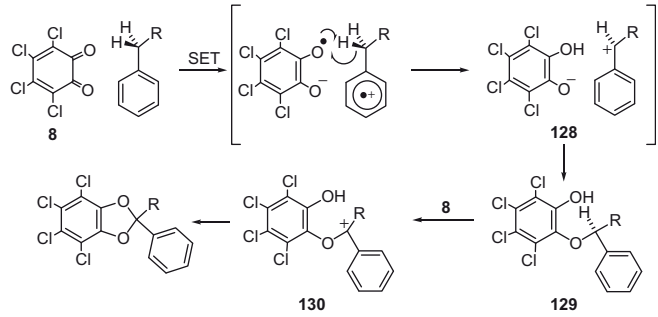
Scheme 32



Scheme 33

2,3-diphenyl-3*H*-quinazoline-4-thione gave **121** (81IJB118) and xanthene-9-thiones gave **122** and **123** (59CJC863, 84LA196). Yields tend to be moderate to good and typical conditions involve heating in the range of 80–200 °C, usually in a solvent. A high-potential quinone appears to be necessary for this type of reaction but the mechanism of sulphur elimination is not clear.

3.1.3.4 Dehydrogenation. The high-potential tetrahalo-1,2-benzoquinones oxidise allyl, benzyl and related CH groups to give 1,3-benzodioxoles. Representative examples are given in Scheme 33. An early example was the oxidation of 2,5-dimethylhexa-2,4-diene to give the dioxole **124** (69CC1096), but further examples of allyl oxidation do not appear to have been reported. A number of examples of oxidation of benzyl derivatives are known. These include toluenes, disubstituted methanes (e.g. **125**), cyclopropenes and



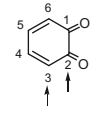
Scheme 34

indane (83MI343, 99JCM626, 02MOL840, 03SC3997), and also 2-phenyl-1,3-dihydro-isoindole (95JCM498), tetralones (e.g. **126**) (68CJC3625, 70JCS(C) 1257) and naphthols (e.g. **127**) (84TL2253, 92T8841), and their heterocyclic analogues (70CJC327, 88T7265, 88IJB605). Kenner and co-workers characterised a porphyrin derivative by oxidation of a ring methylene by tetrachloro-1,2-benzoquinone to give a stable, crystalline spiroacetal (73JCS (P1)2517).

These oxidations probably occur *via* mechanisms initiated by electron transfer to the quinone. Rahman and Kobayashi have proposed a plausible mechanism of oxidation of benzyl derivatives, which can be extended to other species (02MOL840). They propose formation of an ion pair **128**, probably resulting from initial SET followed by hydrogen atom transfer (Scheme 34). Combination of the ion pair then forms an ether **129** and further oxidation and cyclisation gives the observed product *via* the cation **130**.

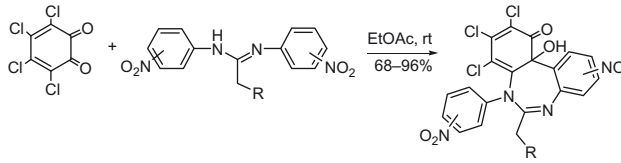
3.1.3.5 Other reactions. A number of other reagents have been reported to give 1,3-benzodioxole products by addition–elimination reactions in the manner described in Sections 3.1.3.1–3.1.3.4. These include hydrazones (59JOC1883), nitroalkanes (87TL3975), enamines (04M1557), dichloromethane (05OL2567) and benzoimidazolium iodides (07RJO220). Friedrichsen and co-workers have demonstrated similar reactions of the furan ring of isobenzofurans and thieno[2,3-*c*]furans in which the eliminated group can be regarded as a ketone formed from the furan ring (69TL1219, 89CB1119).

3.1.4 Reaction at C2 and C3



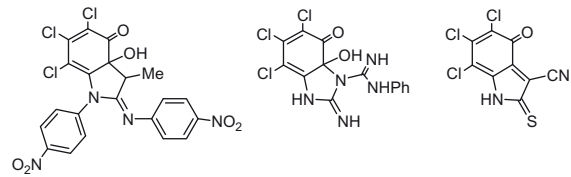
Reactions at positions C2 and C3 fall into two categories: (a) reactions of 3,4,5,6-tetrachloroquinone in which the 3-chloro group is substituted by a nucleophilic centre followed by cyclisation at C2 and (b) reactions of 3-unsubstituted *ortho*-quinones with thiols or thiophenols, which preferentially react at C3, followed by cyclisation at C2.

3.1.4.1 Reactions of 3,4,5,6-tetrachloroquinone. This mode of reaction is conveniently illustrated by N^1,N^2-dinitroarylamidines, which give the dibenzodiazepine derivatives **131** in good yield (equation (17)) (03T5887). In the case of the di-*para*-nitrophenylamidine (R=Me) the tetrahydroindol-4-one **132** was also formed as a minor product (23%). Using 1-phenylbiguanide the similar five-membered ring product **133** (23%) was obtained (04HAC63). Reaction with cyanothioacetamide in hot ethanol in the presence of piperidine resulted in the elimination of water and formation of the product **134** (99JCM626). 2-Methylquinolines and 2-methylquinoxalines react in a similar manner (70CJC327) and ylidene-*N*-phenylhydrazine carbothioamides (PhNH.CS.NHN=CHR) give indazole derivatives in good yield after *in situ* reduction and elimination of water (07ARK265).



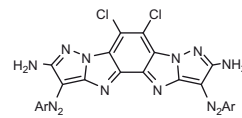
(17)

131 (R = H, Me)



132 **133** **134**

With some reagents a second reaction at positions C1 and C6 occurs. Thus 3,5-diamino-4-arylazopyrazoles give the products **135** (96BSB159). Similar behaviour has been observed using ethylenediamine *bis*-benzal (PhCH=NCH$_2$CH$_2$N=CHPh) (97PHA282) and 3-aminopyridin-2-ol (05ZNB999).

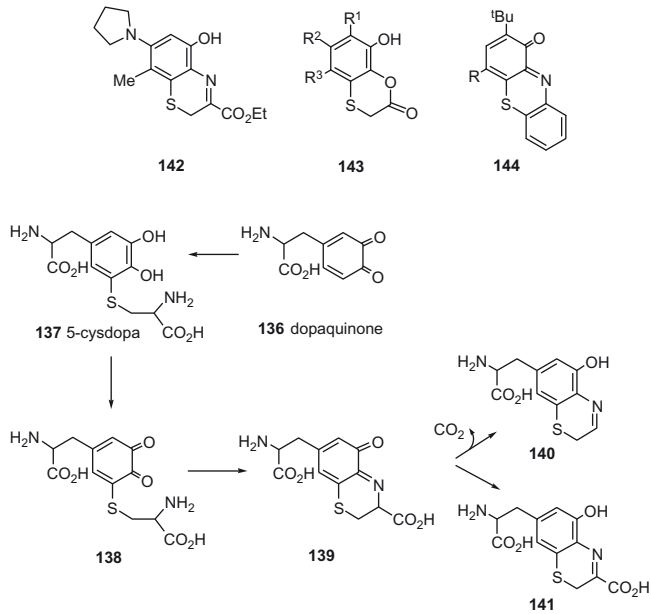


135

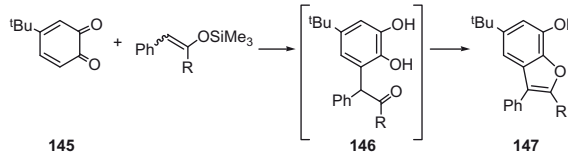
3.1.4.2 Reactions of 3-unsubstituted ortho*-quinones.* The reaction of position C3 of 1,2-benzoquinones with thiols is an important topic since the reaction of cysteine with dopaquinone **136** is an early step in the biosynthesis of phaeomelanin pigment. In particular, cysteine reacts predominantly with dopaquinone to give 5-cysdopa **137** (~74%). This is then oxidised, by redox exchange with dopaquinone **136**, to give the *ortho*-quinone **138**, which cyclises to the imine **139** and then tautomerises, or decarboxylates, to give the 1,4-benzothiazines **140** and **141** (Scheme 35). Benzothiazine rings are characteristic of the yellow to red sulphur-containing phaeomelanin pigments (92MI1, 95BOC193, 06MI282).

Since the heterocycle forming reaction in Scheme 35, and related reactions, is an intramolecular addition–elimination (i.e. **138** → **139**), these reactions should be covered in Section 3.2.1. However, since many examples can be considered as one-pot preparations, they are covered here with appropriate cross-referencing.

In a study of a model aminochrome, cysteine ethyl ester condensed to give the benzothiazine derivative **142**: the corresponding product using cysteine was also formed but was too unstable to be isolated (74T3627). Mercaptoacetic acid gives products of the type **143** (55LA1, 96RJC1847). 2-Aminobenzenethiol reacts with the corresponding *ortho*-quinone, after addition of Fe(III), to give the phenothiazin-1-one **144** (R=Me, Ph, ^{t}Bu) (86JCS(P1)2233). Similar behaviour has been reported using 2-aminophenols (86MI2526, 95MI1720).

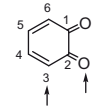


Scheme 35



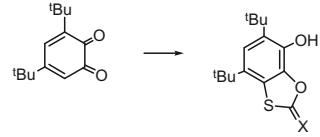
Scheme 36

3.1.5 Reaction at O2 and C3



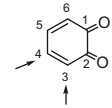
Reaction of 4-*t*-butyl-1,2-benzoquinone **145** with silyl enol ethers, in the presence of catalytic trityl perchlorate, gives the benzofuran derivatives **147** (R=Ph, $PhCH_2$) (Scheme 36), presumably *via* cyclodehydration of the intermediate 1,6-adducts **146** (88CL1105). Use of less-hindered reactants, such as 1,2-benzoquinone and 4-methyl-1,2-benzoquinone, gives 1,4-adducts, which cannot cyclise.

3,5-Di-*t*-butyl-1,2-benzoquinone reacts with potassium dithiocarbonic acid *O*-ethyl ester (EtO-CS_2K) in hot aqueous acetic acid to give benzoxathiol-2-thione **148** (X=S) (83%) (equation (18)) (96RJC1842). A similar reaction using thiourea gives the benzoxathiol-2-one **148** (X=O) (62%) (99MI366), and 4-methoxybenzaldehyde oxime in hot xylene is reported to give a 7-hydroxybenzoxazole (64%) (95RJO984).



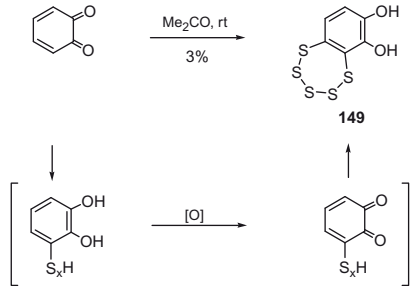
(18)

3.1.6 Reaction at C3 and C4



Reaction of 1,2-benzoquinone with reduced elemental sulphur (H_2S_x) gives a low yield of the pentathiabenzocycloheptene-1,2-diol **149**. A mechanism of formation, summarised in Scheme 37, has been proposed (07JOC2951). The reaction is of some interest because similar cytotoxic natural products contain dopamine fragments and may be derived from the corresponding *ortho*-quinone.

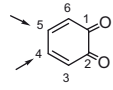
The preferential reaction of H_2S_x at C3 of the *ortho*-quinone (1,6-addition) has been attributed to possible carbonyl hydrogen-bonding by



Scheme 37

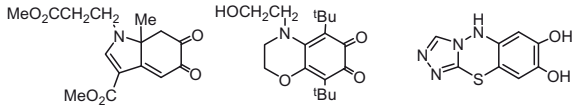
the thiol group. Reagents that lack an ionisable S–H proton tend to react at C4 (1,4-addition) (07JOC2951). This may also explain the preferential reaction of cysteine at the positions adjacent to the carbonyl groups in the phaeomelanin pathway (92MI1).

3.1.7 Reaction at C4 and C5



4-Methylcatechol oxidation (Ag_2O) in the presence of methyl 3-aminopropionate gives the product **150** in very low yield (0.4%): a mechanism of formation involving oxidation to an enamine and addition has been proposed (82HCA1279). Di-*t*-butyl-1,2-benzoquinone reacts with $HN(CH_2CH_2OH)_2$ under oxidising conditions to give the product **151** (00CHC923). Electrochemical oxidation of catechol in the presence of 4-amino-3-thio-1,2,4-triazole is reported to give the product **152** (07MI340). However, the product **152** was not fully characterised and it is not clear why this thiol should preferentially react at position 4 of the benzoquinone when other thiols react at positions 3 and 5 (see Sections 3.1.4.2 and 3.1.6).

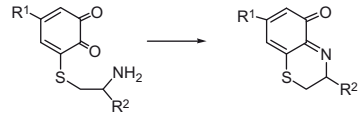
LC–MS studies indicate that tyrosinase oxidation of 4-fluorocatechol gives several products including 2,3-dihydroxy-6-fluorodioxin, formed *via* fluoride displacement from 4-fluoro-1,2-benzoquinone and cyclisation of the resulting 4-(2-hydroxyaryloxy)-1,2-benzoquinone (08MI1).



3.2 Intramolecular addition–elimination

3.2.1 Reactions of 3-substituents (H_2O elimination)

The intramolecular cyclodehydration of *ortho*-quinones with a (2-aminoethyl)thioether substituent at position 3 leads to benzothiazine derivatives (equation (19)) and is an important feature of the biosynthesis of phaeomelanin pigments from 5-cysteinyldopa **137** (Scheme 35). The chemistry of the cyclisation of the quinone **138** and related model compounds has been reviewed (92MI1, 01JPPB123, 06MI282). For further examples see Section 3.1.4.2.

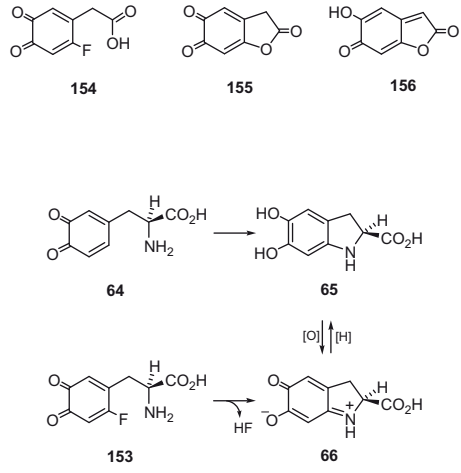


(19)

3.2.2 Reactions of 4-substituents (HF elimination)

An interesting variation on the cyclisation of dopaquinone **64** to give cyclodopa **65** (Section 2.2.1) is the cyclisation of 6-fluorodopaquinone **153**, which gives dopachrome **66** directly by elimination of HF (Scheme 38). Similar cyclisations with fluoride displacement have been observed using the 6-fluoro analogues of dopamine and norepinephrine (87AC1534, 90ABB65).

The quinone **154**, formed by oxidation of 6-fluoro-3,4-dihydroxyphenylacetic acid, cleanly eliminates fluoride giving the quinolactone **155**, which can be interconverted with the quinomethane **156** by choice of conditions (99ABB98). The products **155** and **156** are not stable and give melanin-like polymers.

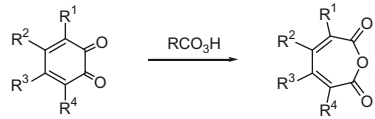


Scheme 38

4. RING-OPENING REACTIONS

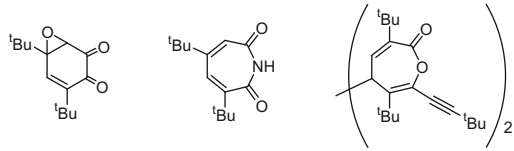
4.1 Ring-expansion reactions

A useful synthetic procedure is the peracid oxidation of 1,2-benzoquinones **1** to the anhydrides **157** (equation (20)), which can be hydrolysed to muconic acid derivatives (48HCA1210). Monoperphthalic acid (51JCS3398, 69JCS(C)2080, 89CC1629) and *m*-chloroperbenzoic acid (80JOC1153, 90JCS(P1)2979) both give good yields of the anhydrides. Perbenzoic acid has also been used (06RJO227). Other oxidising agents tend to give mixtures including the anhydride: reagents that have been investigated include hydrogen peroxide (81JCS(P2)1176), potassium peroxomonosulphate (83CC518) and dioxygen/(bipyridine)(pyridine)iron(III) complex (86JA2921). It is noteworthy that oxidation of 3,5-di-*t*-butyl-1,2-benzoquinone using PhIO and tetraphenylporphinatomanganese(III) chloride catalyst gives the 3,4-epoxide **158** as the major product (61%) (85CL665).



(20)

1 **157**

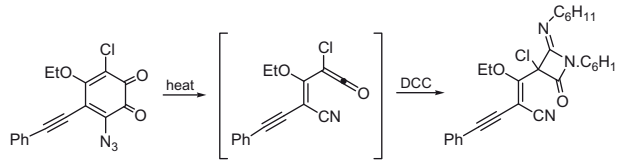


158 **159** **160**

Reaction of 3,5-di-*t*-butyl-1,2-benzoquinone with pyridine cupric methoxychloride and anhydrous ammonia in pyridine gives the imide **159** (~50%) (81JA5795). The lactone dimer **160** is formed in 51% yield from 3,6-di-*t*-butyl-1,2-benzoquinone and 3,3-dimethylbut-1-ynyl-lithium (99MI350).

4.2 Ring-contraction reactions

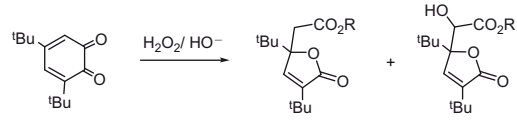
A number of studies of the oxidation of 3,5-di-*t*-butyl-1,2-benzoquinone with hydrogen peroxide (81JCS(P2)1176, 82JOC3766, 83JA5035, 87JOC697) (or reagents that are a source of peroxide (77ACB546, 83CC518, 86JA2921)) have shown that the main products are the acids **161** and **162** (R=H) or the esters **161** and **162** (R=Me, Et), depending on



163 164 165

Scheme 39

the conditions (equation (21)). Similar products have been obtained with 4-*t*-butyl-1,2-benzoquinone (80ACB669).



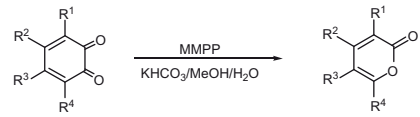
(21)

161 162

Thermolysis (hexane, reflux) of the quinone **163** in the presence of dicyclohexylcarbodiimide (DCC) gives the lactam **165** (44%), providing evidence that the initial product, after eliminations of CO and N_2, is the ketene **164** (Scheme 39) (86JOC419).

4.3 New six-membered rings

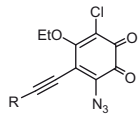
Oxidation of 4-alkylamino-5-methoxy-1,2-benzoquinones by magnesium monoperoxyphthalate (MMPP) gives pyran-2-ones (equation (22)) in moderate to good yield (95TL6669). Similar transformations have been observed using methoxy(pyridine)copper(II) chloride in pyridine (80JOC4210). Pyran-2-one products have been obtained by oxidation of *ortho*-quinones with other reagents, including potassium peroxomonosulphate (83CC518), hydrogen peroxide (81JCS(P2)1176) and (bipyridine)(pyridine)iron complex (86JA2921), but a number of other oxidation products are usually formed and these reactions are not synthetically useful.



(22)

Thermolysis of the azide derivatives **166** and **167** leads to novel heterocyclic products, which are formed by elimination of CO and N_2 (*cf*

Scheme 39) and intramolecular cyclisation to give new ring systems, for example **168** (87TL5013, 87JOC2530).



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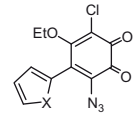
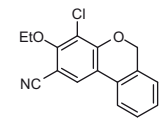


167



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CHAPTER 2

Naturally Occurring Nitrogen–Sulfur Compounds Part 2. 1,4-Thiazine and Benzo-1,4-Thiazine alkaloids☆

Catherine L. Lucas and **Christopher J. Moody**

Contents

☆Part 1, Naturally occurring nitrogen–sulfur compounds. The benzothiazole alkaloids (09AJC639).

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1. INTRODUCTION

A great many naturally occurring substances that contain heterocyclic rings, including alkaloids and antibiotics, derive in Nature from α-amino acids. One particular subset of these heterocyclic natural products is one that contains both nitrogen and sulfur atoms, and over the years, a number of such N,S-containing compounds have been discovered, attracting the attention of biological and synthetic chemists alike. These fascinating natural products include the 1,4-thiazines and their di- and tetrahydro and benzo derivatives, the subject of this short review.

1,4-Thiazine containing alkaloids are relatively rare in Nature, but they range in structural complexity from simple monocyclic derivatives such as chondrine and benzothiazines such as the aplidinones, to more complex tri- and polycyclic compounds exemplified by ansathiazin and the shermilamines. On the other hand, the simplest N,S-heterocycle – the 5-membered thiazole – is relatively common in Nature, and, for example, plays a vital role in the function of thiamine (vitamin B_1). Thiazole rings also occur in important biologically active natural products such as the epothilones (Figure 1).

Although the biosynthesis of 1,4-thiazines has not been studied in detail in many cases, the evidence suggests that they are mainly derived from cysteine or its derivatives. For example, it was shown in the 1960s that cycloalliin **3**, a 1,4-thiazine monoxide isolated from the onion *Allium cepa*, is biosynthesized from cysteine *via* the carboxypropyl and propenyl

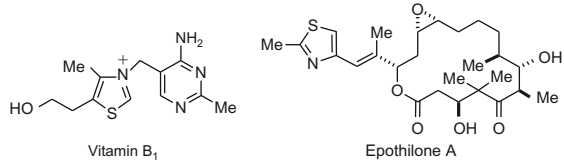
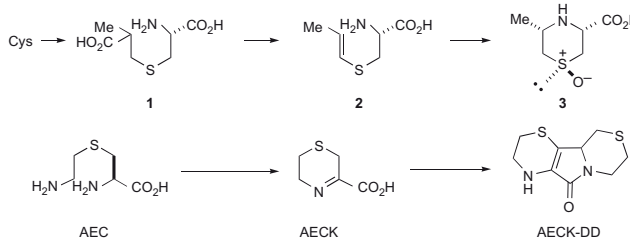


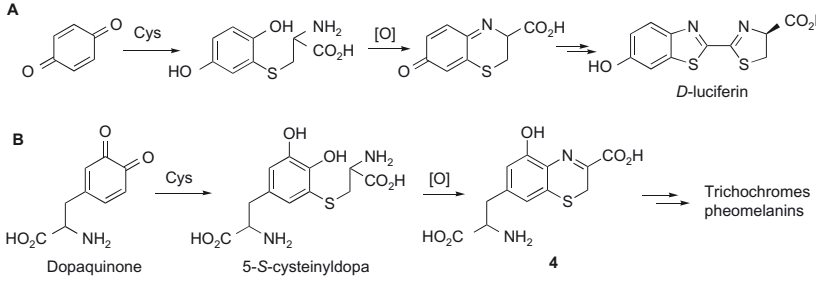
Figure 1 Thiazole natural products: structures of thiamine (vitamin B_1) and the anticancer compound epothilone A.

derivatives **1** and **2** (Scheme 1), although the exact stage at which the *S*-oxidation occurs remains unclear (65ACSA2257, 67ACSA1654). An interesting case is that of aminoethylcysteine ketimine (2*H*-5,6-dihydro-1,4-thiazine-3-carboxylic acid), the product of enzymatic deamination and cyclization of *S*-aminoethylcysteine (AEC) (04T4151). The compound dimerizes rapidly, with loss of carbon dioxide, to give the tricyclic compound known as aminoethylcysteine ketimine decarboxylated dimer (AECK-DD) (Scheme 1), a compound found in human plasma and urine.

Benzo-1,4-thiazines also derive from cysteine, often by addition to benzoquinones. The reaction was originally investigated in the biosynthesis of firefly luciferin and of the characteristic pigments of red hair, the trichochromes. It was proposed by McCapra and coworkers that addition of cysteine to benzoquinone was followed by oxidative cyclization to the benzothiazine, which in the case of luciferin then undergoes ring contraction to the benzothiazole (Scheme 2A; 75JCS(CC)42). Similarly, addition of cysteine to dopaquinone, followed by oxidative cyclization of 5-*S*-cysteinyldopa to benzothiazine **4**, leads into the trichochrome–pheomelanin pathway (Scheme 2B) (96JOC598, 99JOC3009, 01JOC6958). Similar additions of cysteine to benzoquinones, followed by oxidative cyclization have been proposed in the biosynthesis of rifamycin verde (from rifamycin S) (80JAN842), and of shermilamine B (93T6223).



Scheme 1 Proposed biosynthesis of cycloalliin **3** and AECK-DD.



Scheme 2 (A) Proposed involvement of benzo-1,4-thiazines in biosynthetic route to firefly luciferin; (B) biosynthesis of benzothiazine **4**, a precursor to the red hair pigments, the trichochromes and pheomelanins.

2. DI- AND TETRAHYDRO-1,4-THIAZINES AND THEIR *S*-OXIDES

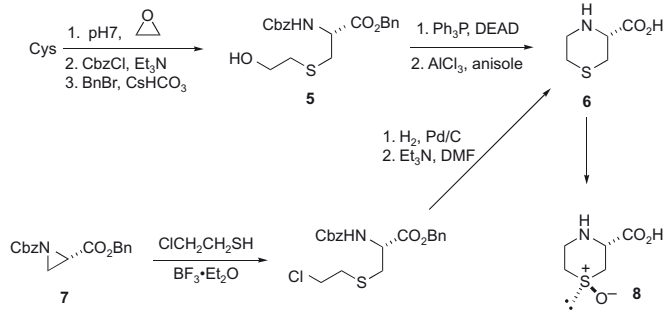
The general chemistry, reactivity and methods of synthesis of 1,4-thiazines have been covered in a recent comprehensive treatise (08CHEC(8) 607).

2.1 Deoxychondrine

Deoxychondrine, also known as chordarine, was first isolated from the marine alga *Heterochordaria abietina* in 1977, and assigned as (*R*)-tetrahydro-1,4-thiazine-2-carboxylic acid **6** (77MI03). A number of routes to this simple natural product have been reported. For example, reaction of cysteine with ethylene oxide at pH 7 followed by protection of amino and carboxyl groups gave the cysteine derivative **5**. Cyclization under Mitsunobu conditions established the 1,4-thiazine ring, subsequently deprotected under forcing conditions to give deoxychondrine **6** (Scheme 3) (94ACSA517). Alternatively, reaction of the enantiomerically pure aziridine **7** with 2-chloroethanethiol, followed by deprotection and cyclization gave deoxychondrine **6** (Scheme 3) (87BCJ2963).

2.2 Chondrine

Chondrine **8**, the sulfoxide of deoxychondrine, was isolated from the red alga *Chondria crassicaulis* (60MI01), and subsequently from the brown alga *Undaria pinnatifida* (63MI02). The structure was determined using a series of chemical degradations – deoxygenation to deoxychondrine and Raney nickel desulfurization to *N*-ethylalanine. The stereochemistry of the natural material is (1*S*,3*R*), and the axial nature of the sulfoxide was confirmed by X-ray crystallography (72AX(B)2789). Unsurprisingly, the simplest synthetic route to chondrine involves *S*-oxidation



Scheme 3 Synthesis of deoxychondrine **6** and its oxidation to chondrine **8**.

of deoxychondrine, and this is readily achieved using aqueous hydrogen peroxide in acetic acid. The oxidation is diastereoselective (*de* = 66%) and it gives the axial sulfoxide as the major product (Scheme 3) (70JOC1594).

2.3 Cycloalliin

Cycloalliin **3** (Scheme 1) is the most abundant sulfur-containing compound in the onion *Allium cepa*, and was first isolated in the 1950s (59ACSA623), and the stereochemistry and axial sulfoxide was confirmed by crystallography (72AX(B)2615). The compound has been synthesized from *S*-allylcysteine by addition of HBr across the alkene, cyclization in pyridine and final *S*-oxidation (59ACSA623), although the stereochemical outcome of these transformations was not clear. The oxidation step, with formation of the desired axial sulfoxide, was subsequently investigated by other workers (70JOC1594).

2.4 Tetrahydro-1,4-thiazine-3,5-dicarboxylic acid

This 1,4-thiazinedicarboxylic acid **9** (Figure 2) has been detected in human urine and closely related compounds have been detected in mammalian brains, although their biochemical significance remains obscure. The compound was first prepared many years ago, presumably as a mixture of diastereomers (37JA801), although the synthesis has been revisited more recently. Reaction of (*R*)-cysteine methyl ester with racemic 2,3-dibromopropionate gave a 1:1 mixture of diastereomeric thiazines, chromatography of which gave the pure *trans*-(*R*,*R*)-diastereomer (90JHC1661).

2.5 3,4-Dihydro-6-(4-hydroxyphenyl)-1,4-thiazine-1,1-dioxide

The sulfone group is relatively rare in natural products, but a simple example is the 1,4-thiazine-1,1-dioxide **10** (Figure 2), isolated from the marine sponge *Anchinoe tenacior* (94TL2421). The structure was assigned on the basis of NMR spectroscopy, but has yet to be confirmed by synthesis.

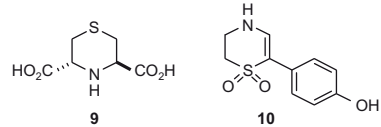


Figure 2 Structures of tetrahydro-1,4-thiazine-3,5-dicarboxylic acid **9** and 3,4-dihydro-6-(4-hydroxyphenyl)-1,4-thiazine-1,1-dioxide **10**.

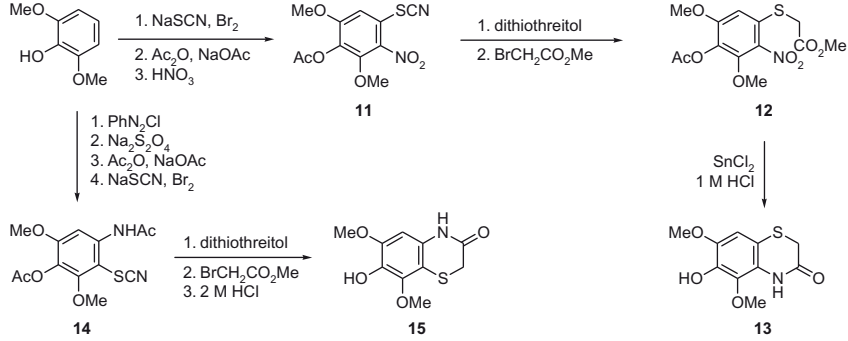
3. BENZO-1,4-THIAZINES

3.1 Antibiotic BMY 40662

During a large scale fermentation of the anticancer agent esperamicin A_1, a new antibiotic designated BMY 40662 was discovered (90JAN107). After detailed NMR spectroscopic investigations, the antibiotic was assigned as 6-hydroxy-5,7-dimethoxybenzothiazin-3-one **13**. This compound was synthesized some 3 years later by Kelly et al. starting from 2,6-dimethoxyphenol (Scheme 4) (93JOC5855). Thus electrophilic thiocyanation, followed by acetylation and nitration gave the pentasubstituted benzene **11**. Reduction with dithiothreitol gave the corresponding thiol that was directly alkylated with bromoacetate to give **12**. Finally, reaction with tin(II) chloride in hydrochloric acid resulted in reduction of the nitro group, spontaneous cyclization and deacetylation to give the benzothiazinone **13** (Scheme 4). However, the spectroscopic properties of the synthetic compound **13** were different to the natural product, and after reexamination of the original spectroscopic data, the isomeric benzothiazinone structure **15** was proposed. This was then synthesized by reversing the order of the two electrophilic substitutions, and data for the resulting benzothiazinone **15** was a much closer match for the natural product, suggesting that the structure of the antibiotic BMY 40662 should be revised to **15** (93JOC5855). The simpler compound 7-hydroxybenzothiazin-3-one is also claimed to be a natural product, although details have only been reported in a thesis (03MI06). The compound has been synthesized as part of medicinal chemistry programs (87JMC295).

3.2 The xanthiazones

Plants of the *Xanthium* genus, commonly known as burweed or cocklebur, belong to the large Asteraceae family, and have been widely



Scheme 4 Synthesis of antibiotic BMY 40662.

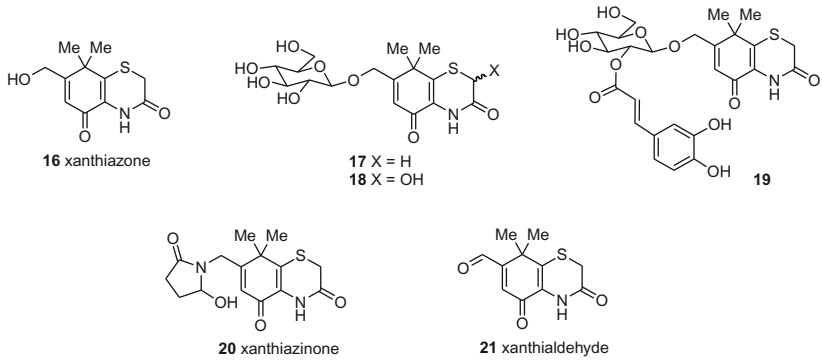


Figure 3 Structures of the *Xanthium* benzothiazine natural products.

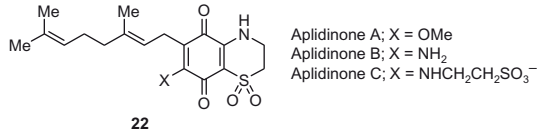


Figure 4 Structures of the aplidinones.

used as a source of traditional medicines. Detailed investigation of the acetone extracts of the fruits of *Xanthium strumarium* revealed a highly unusual benzothiazine derivative. X-ray crystallography determined the structure as 7-hydroxymethyl-8,8-dimethyl-4,8-dihydrobenzo[1,4]thiazine-3,5,-dione **16** (Figure 3), a compound named as xanthiazone (98P1083). Subsequently the *O*-*β*-D-glucopyranoside derivative **17** was isolated (05MI07), along with the unusual thiohemiacetal glucopyranoside **18** (06MI08) and the 2-*O*-caffeoylglucopyranoside **19** (06MI09). More recently the hydroxypyrrolidinone compound **20**, named xanthiazinone (08MI10), and the aldehyde corresponding to **16** (08MI11) have also been isolated. None of this family of compounds has been synthesized to date.

3.3 The aplidinones

Another group of naturally occurring benzothiazines that are yet to succumb to synthesis is the aplidinones **22** (Figure 4). These compounds isolated from the Mediterranean ascidian *Aplidium conicum*, incorporate a geranyl side chain and are clearly of mixed biosynthetic origin. The structures were determined by NMR spectroscopy with the regiochemistry of the thiazine ring being assigned on the basis of DFT calculations of ^{13}C chemical shifts (05EJO5024). The aplidinones are structurally related to the conicaquinones and thiaplidiaquinones (q.v.), isolated from the same marine organism.

3.4 The thiazinotrienomycins and antibiotics TMC-135A and TMC-135B

In 1995, Hosokawa and coworkers reported the isolation of five new ansamycin antibiotics, thiazinotrienomycins A–E (Figure 5) (95JAN471). These complex structures were determined by detailed NMR spectroscopic studies and contain a benzo[1,4]thiazinone core with a triene containing ansa chain bridging positions 6 and 8, although the stereochemistry was not specified. The compounds share the same ansa chain as the related antibiotics trienomycin A and mycotrienins I and II, and the benzothiazole-containing thiazinotrienomycins F and G. All five thiazinotrienomycins (A–E) show growth inhibitory activities against human cancer cell lines, with thiazinotrienomycins A and B showing very strong toxicity against cervical cancer cell lines (00JAN306). It is interesting to note that the compounds exhibiting the strongest cytotoxicities are thiazinotrienomycins A and B, compared to thiazinotrienomycins C, D and E with the opposite regiochemistry of the thiazinone ring.

The relative and absolute stereochemistry of (+)-thiazinotrienomycin E was subsequently determined using a combination of degradation experiments and spectroscopic methods (98TL2891), thereby paving the way for the first total synthesis from the group of Amos B. Smith III. The key steps in the synthesis are outlined in Scheme 5, and comprise Mukaiyama macrolactamization, Kocienski-modified Julia olefination and sulfone alkylations (99OL1491, 00JOC3738).

The key intermediate benzothiazine **25** was accessed *via* displacement of fluoride in the dinitrobenzene **23** with the lithium salt of methyl thioglycolate to provide thioether **24**, which after tin(II)-mediated reduction of the nitro groups and cyclization furnished benzothiazine **25** in modest yield (Scheme 6). It was noted by the authors that other methods of reduction such as hetero- or homogenous hydrogenation did not improve the yields for this step. It is also noteworthy that subsequent chemoselective reduction of the ester group to give the requisite alcohol proved problematic due to the ease of reduction of the benzothiazinone amide functionality.

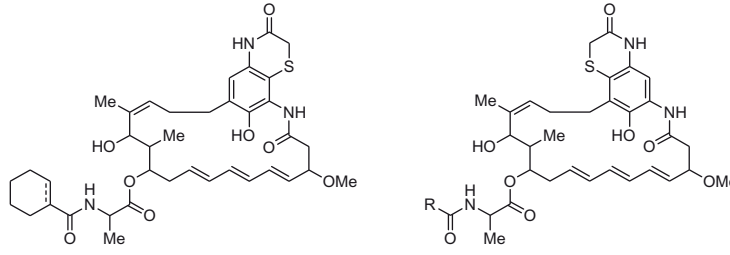
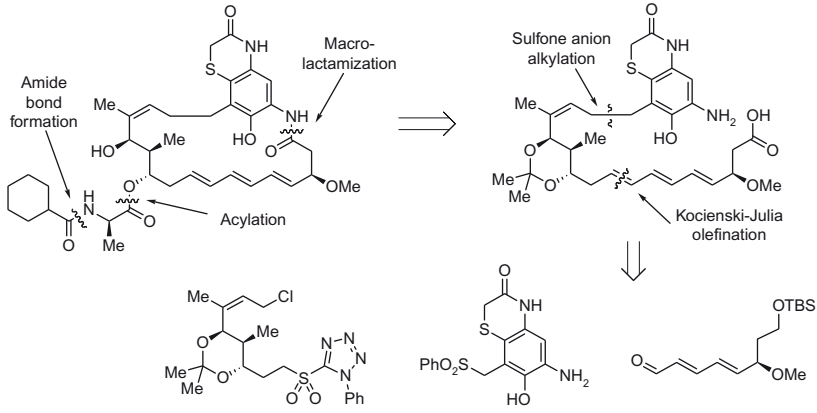
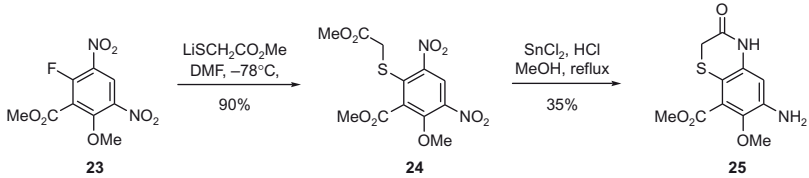


Figure 5 Structures of the thiazinotrienomycins.



Scheme 5 Retrosynthesis of thiazinomycin E.



Scheme 6 Synthesis of the benzothiazinone core of thiazinotrienomycin E.

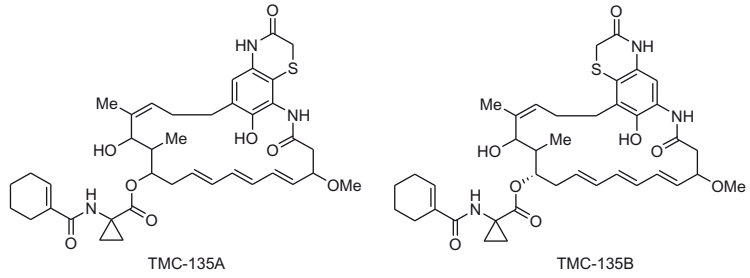


Figure 6 Structures of the TMC-135 antibiotics.

Five years later, two new benzothiazinone ansamycin antibiotics TMC-135A and -135B were also isolated from a *Streptomyces* strain by Nishio and coworkers (Figure 6) (00JAN724). These compounds are closely related to thiazinotrienomycins A and D, only differing in the substitution of the amide side chain. Again it is interesting to note that TMC-135A showed 10 times greater cytotoxic activity than TMC-135B, showing that the pattern of substitution of the benzothiazinone moiety is important to maintain good levels of biological activity.

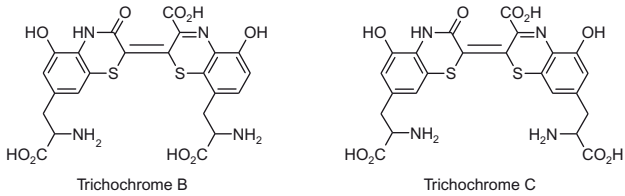


Figure 7 Structures of the dimeric benzothiazines, trichochromes B and C.

3.5 The trichochromes

The characteristic pigments of human red hair, the pheomelanins, have been studied for more than a century, and major contributions have been made in the last four decades from the Naples school led by Prota and, more recently, Napolitano. Although the involvement of benzo-1,4-thiazines was first suggested 40 years ago, the subject is still a matter of study, with a recent work suggesting that benzothiazoles rather than benzothiazines may be involved in the hair pigments (08MI12). Nevertheless, the early stages in the biosynthesis of these heterocyclic pigments seem clear as outlined in Scheme 2B. Addition of cysteine to dopaquinone, followed by oxidative cyclization of 5-*S*-cysteinyldopa to benzothiazine **4** leads by oxidative dimerization to the trichochromes, exemplified by trichochromes B and C (Figure 7) (96JOC598, 99JOC3009, 01JOC6958).

4. TRICYCLIC THIAZINES

Many of the naturally occurring tricyclic thiazines are essentially naphtho analogues of the benzothiazines discussed in the previous section, and are isolated mainly from bacterial or marine sources, although the best-known tricyclic thiazine is the phenothiazine chlorpromazine. This compound, 2-chloro-10-(3-dimethylaminopropyl)phenothiazine developed in the early 1950s was one of the first antipsychotic drugs on the market, and although it is claimed to be a natural product (03MI05), the evidence is extremely weak, and therefore it is not included here.

4.1 The conicaquinones and ascidiathiazones

Marine invertebrates have proved to be a rich source of biologically active prenylated heterocyclic natural products, with several prenylated quinones and chromenols having been discovered from ascidian species (sea squirts). Conicaquinones A and B (Figure 8) were isolated from the marine ascidian *Aplidium conicum* in 2003 (03EJO898), and are clearly related to the previously mentioned benzoquinone thiazine counterparts, the aplidinones (05EJO5024). However, unlike the aplidinones, these

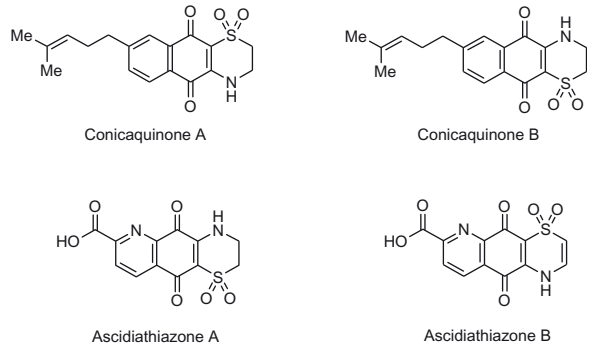
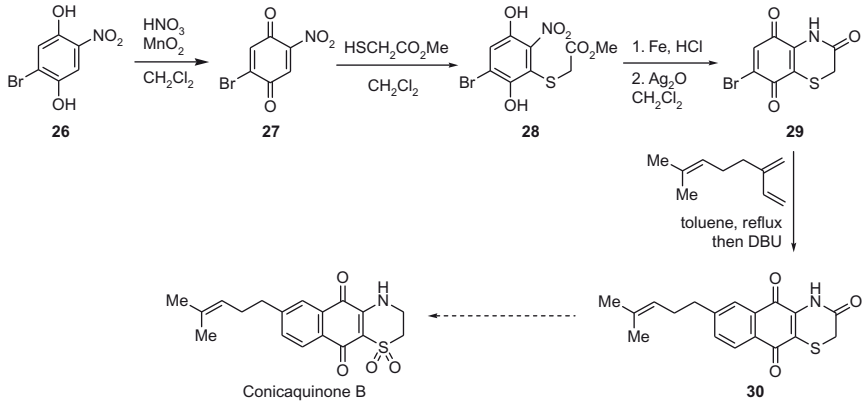


Figure 8 The conicaquinones and ascidiathiazones.

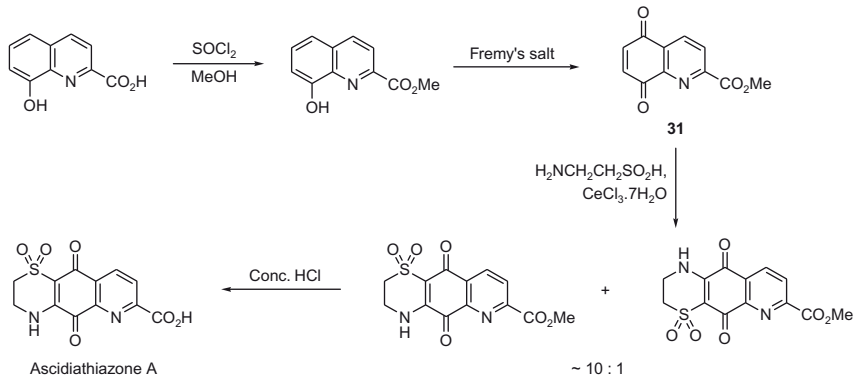


Scheme 7 Approach to the synthesis of the naphthoquinone thiazine dioxide conicaqunone B.

naphthoquinone derivatives occur as both regioisomers of the thiazine ring. The compounds showed moderate cytotoxicity.

Although the conicaquinones are yet to be synthesized, Tapia et al. have recently reported an interesting approach based on a regioselective Diels–Alder reaction (Scheme 7), although confusingly the authors referred to the natural products as conaquinones (07S3773). Thus oxidation of the hydroquinone **26** gave the unstable quinone **27** that was immediately trapped with methyl thioglycolate in high yield. Reduction of the nitro compound **28** with iron and hydrochloric acid was followed by cyclization to the benzothiazinone, oxidation of which gave quinone **29**. The key Diels–Alder reaction with myrcene proceeded with high regioselectivity to give, after DBU-induced aromatization, the naphthoquinone thiazinone **30**, a precursor to conicaquinone B (Scheme 7).

The same species of *Aplidium* also yielded ascidiathiazones A and B (Figure 8) a few years later (07JNP936), interestingly again containing



Scheme 8 Synthesis of ascidiathiazone A.

both regiochemistries of the thiazine ring. These unusual thiazine–quinoline–quinone structures were confirmed by X-ray crystallographic analysis of ascidiathiazone A. The synthesis of the natural product was completed in four steps from 8-hydroxyquinoline-2-carboxylic acid by regioselective addition of hypotaurine to quinoline-quinone **31** formed by Fremy's salt oxidation (Scheme 8). Ascidiathiazones A and B exhibited interesting biological activity as anti-inflammatory agents, showing inhibition of neutrophil superoxide production *in vitro* with IC_{50} values of 1.55 and 0.44 μM, respectively (08BMC9432).

4.2 Ansathiazin

Ansathiazin, also known as antibiotic TAN-528B, was isolated from a culture of *Streptomyces albolongus* by Tanida et al. in 1986, as a minor product alongside the known antibiotic awamycin (TAN-528A) (Figure 9) (86E1167). The structure features oxidation at the same position of the thiazine ring as in the benzothiazines TMC-135A and -135B and thiazinotrienomycins discussed in the previous section. A full stereochemical determination of the structure of awamycin was conducted by Herlt et al. using X-ray crystallography (92AJC309). It is therefore assumed that awamycin constitutes a biosynthetic precursor to ansathiazin and that they share the same stereochemistry of the macrocycle. Roush and Coffey have synthesized the naphthoquinone core of awamycin (95JOC4412), although no synthetic studies toward ansathiazin itself have been reported to date.

4.3 FR901537

The novel aromatase inhibitor FR901537 was isolated from a cultured broth of *Bacillus* sp. No. 3072 in 1995 by Oohata and coworkers (95JAN757). Aromatase, a cytochrome P450 enzyme, is important in

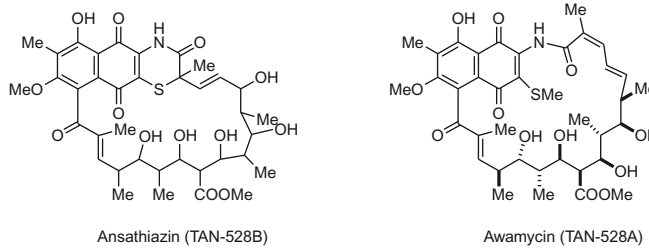


Figure 9 The ansamycin antibiotics ansathiazin and awamycin.

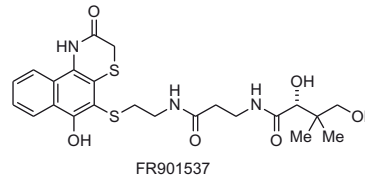


Figure 10 Structure of the aromatase inhibitor FR901537.

estrogen biosynthesis, and therefore aromatase-specific inhibitors may be an effective treatment for estrogen-dependent tumors such as breast cancer, endometrial cancer and prostate cancer. The compound displays potent antitumor effects against estrogen-dependent mammary tumors in a postmenopausal tumor model (95JAN763). The structure (Figure 10) was deduced by NMR spectroscopic analysis and it was proposed that FR901537 had a novel tricyclic structure, composed of a naphthol unit fused to a thiomorpholinone ring, with a pantetheine side chain. It is proposed that the stereochemistry of the side chain is the same as in pantetheine itself, although no details of this assignment of stereochemistry were reported. In common with many other naturally occurring thiazines, FR901537 has not been synthesized.

4.4 The euthyroideones

As mentioned previously, marine invertebrates have proved to be a rich source of biologically active heterocyclic natural products, and bryozoans fall into this category. The most well-known bryozoan secondary metabolites isolated to date are the bryostatins, highly potent antineoplastic agents (00BMC1841). The euthyroideones were isolated from New Zealand marine bryozoan *Euthyroides episcopalis*, and were found to have novel isoquinoline–thiazine–quinonemethide tricyclic structures (98JOC9545). X-ray crystallographic analysis of crystals of euthyroideone A allowed the complete structure to be determined. Comparison of these data with the spectroscopic data for euthyroideones B and C, together

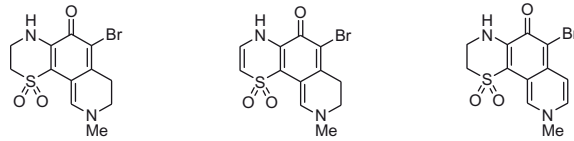


Figure 11 The euthyroideones.

with further NMR correlation experiments facilitated the determination of the other two structures (Figure 11). Only two assays were conducted on each compound due to lack of material, with none of the three compounds exhibiting significant activity against either P388 murine leukemia cells or in antiviral/cytotoxicity assay systems.

5. POLYCYCLIC THIAZINES

In this section we examine structurally complex thiazines, where the heterocycle forms part of a polycyclic system. Many of these fascinating natural products also contain quinone chromophores, and in many cases the corresponding compound lacking the thiazine ring also occurs in Nature. Hence it appears that the thiazine ring is added late in the biosynthetic pathway, presumably by addition of cysteine, cysteamine or hypotaurine to the quinone.

5.1 The adociaquinones and alisiaquinone C

The first heterocycles in this category, the adociaquinones, are prime examples of the aforementioned situation where the parent compound lacking the thiazine ring also occurs naturally. The pentacyclic polyketide furanoquinones halenaquinone and xestoquinone (Figure 12) were isolated in the 1980s from the marine sponge *Xestospongia* by U.S. and Japanese groups, respectively (83JA6177, 85CL713). Both compounds have been subjected to synthetic studies, notably by Harada and coworkers (88JA8483, 90JOC3158); the synthesis also confirms the absolute stereochemistry of the natural products. The corresponding thiazine dioxide derivatives of xestoquinone and halenaquinone, adociaquinones A and B, and their oxidized keto derivatives were isolated from a marine sponge of the *Adocia* species found in the Truk Lagoon, a sheltered lagoon in the ocean north of Papua New Guinea (88JOC3922). It would appear that if indeed these compounds derive in Nature by addition of cysteine, cysteamine or hypotaurine to the quinone, this addition is not regioselective since both regioisomers of the thiazine ring occur.

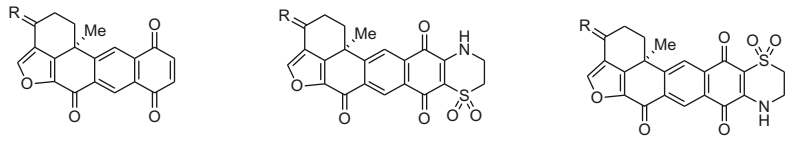
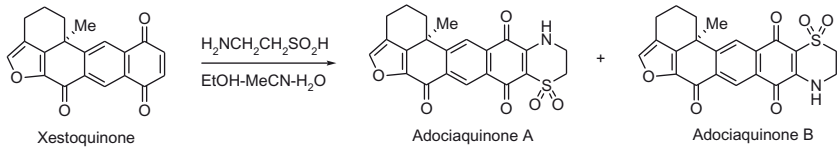


Figure 12 The adociaquinones and their putative biosynthetic precursors, xestoquinone and halenaquinone.



Scheme 9 Conversion of xestoquinone into adociaquinones A and B.

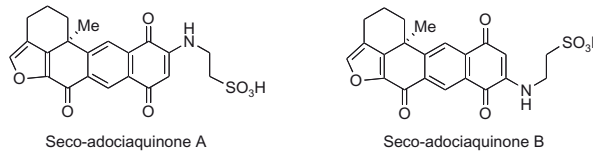


Figure 13 Seco-adociaquinones A and B.

Both the groups of Schmitz and Harada have converted xestoquinone into adociaquinones A and B by reaction with hypotaurine, the former group using natural starting material, and the latter group using synthetic material of known absolute configuration, hence confirming the stereochemistry of the adociaquinones (Scheme 9). In neither case was the chemical addition of hypotaurine regioselective.

Subsequent investigation of the methanol extract of the *Xestospongia* sponge revealed the presence of two further derivatives, seco-adociaquinones A and B (Figure 13) (95JMC4503). The isolation of these compounds suggests that in the biosynthesis of the adociaquinones, the C–N bond is formed first by addition of the amino group of the N–C–C–S fragment. A range of biological activities have been reported for these heterocyclic natural products including inhibition of topoisomerase II (95JMC4503) and Cdc25B phosphatase (05BMC999).

Isolated from a New Caledonian deep-water sponge, alisiaquinones A–C and alisiaquinol are related to the aforementioned compounds, but show a unique substitution pattern in the furan ring (08JNP1189). All four compounds displayed promising activity against two enzymatic targets in *Plasmodium falciparum*, and hence are potentially important in the control of malaria. Only the relative stereochemistries

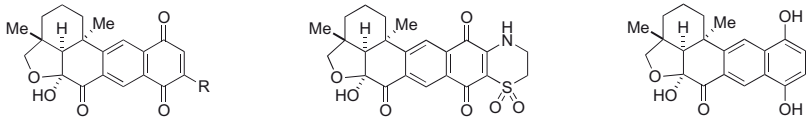


Figure 14 The alisiaquinones.

of the compounds were assigned by the analysis of the spectroscopic data. However, it seems reasonable to suggest that the absolute stereochemistry of the natural products would match that of the adociaquinones, halenaquinone and xestoquinone as indicated in Figure 14.

5.2 Xestoquinolide B

Xestoquinolides A and B were isolated from a *Xestospongia* sponge by Alvi and coworkers alongside the related compounds xestoquinone and halenaquinone discussed previously (93JOC4871), xestoquinolide B being the hypotaurine adduct of xestoquinolide A (Figure 15). The compounds are related to xestoquinone and adociaquinones A and B, but feature an expanded 7-membered lactone fused to a methyl-substituted cyclohexene, in place of the cyclohexane–furan–cyclohexanone tricyclic system. The authors report that the regiochemistry of the thiazine ring could not be unambiguously determined, even by comparison of the NMR spectroscopic data with that of adociaquinones A and B. Hence this issue remains to be resolved by synthesis. Xestoquinolide A showed moderate inhibition of protein tyrosine kinases, a family of enzymes involved in the regulation of cell growth and signaling, which has been associated with cancer and psoriasis. The thiazine analogue, xestoquinolide B showed no activity using the same assay.

5.3 The shermilamines A–E and cycloshermilamine D

The shermilamines are a group of pentacyclic alkaloids based on the well-known pyrido[4,3,2-*mn*]acridine framework (Figure 16) (03MI04). The

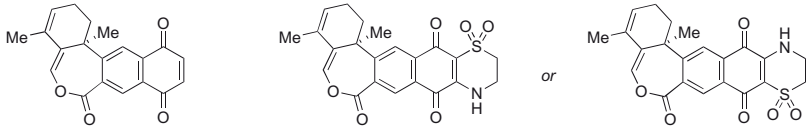


Figure 15 The xestoquinolides.

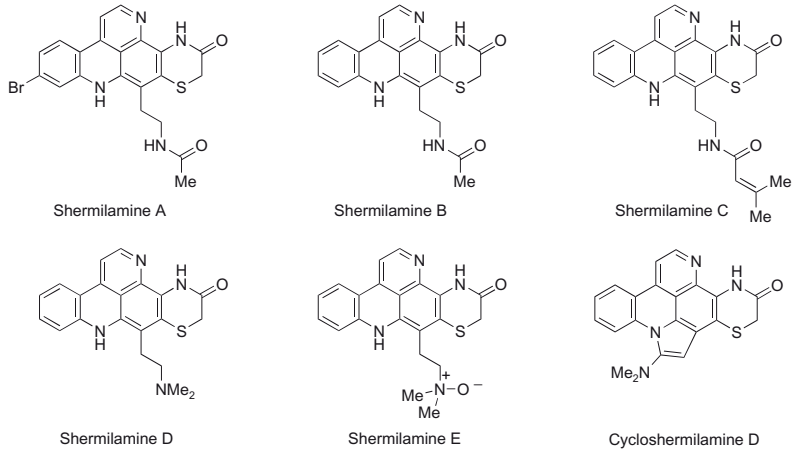
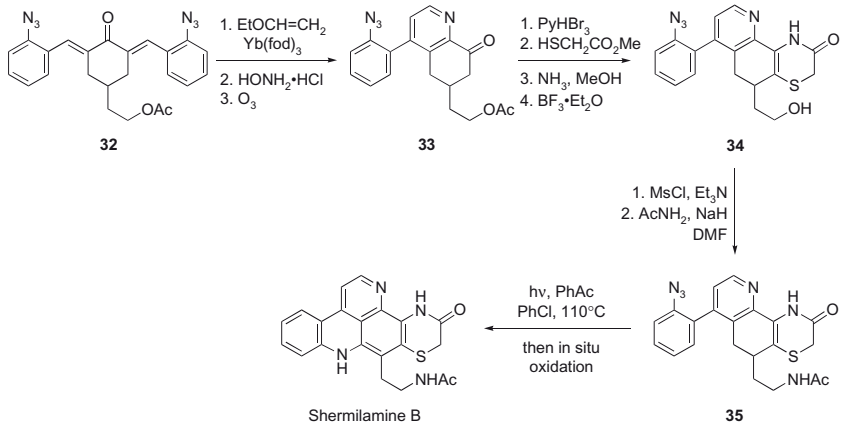


Figure 16 Structures of the shermilamines, thiazinone pyrido[4,3,2-*mn*]acridine alkaloids.

first compound in the series, the orange shermilamine A, was isolated from the purple colonial tunicate *Trididemnum* sp. collected from Guam (88JOC4619), the structure being determined by X-ray crystallography. A year later, in 1989, the structure of the debromo analogue, shermilamine B, was published independently by two groups. Scheuer and coworkers isolated the compound during their further investigation of the tunicate *Trididemnum* sp. (89JOC4231), while Rudi and Kashman isolated the same compound from the purple Red Sea tunicate *Eudistoma* sp. (89JOC5331). Shermilamine C, isolated from a Fijian *Cystodytes* sp. ascidian, shares the same pentacyclic core as shermilamine B, and only differs in the presence of the dimethylacrylamide side chain in place of the acetamide (94JMC3819). Another purple tunicate *Cystodytes violatinctus* gave rise to shermilamines D and E (98JOC4601), and the same organism was the source of final member of the series, cycloshermilamine D (00JNP830).

The first synthesis of a shermilamine alkaloid was achieved by Ciufolini's group in 1995, and formed part of an elegant general strategy toward other pyridoacridine alkaloids such as the diplamines, cystodytins, kuanoniamines and dercitins (95JA12460, 95TL4709). The strategy involved a catalyzed Diels–Alder reaction of symmetrical enone **32** with ethyl vinyl ether followed by elaboration of the resulting tetrahydropyran into a pyridine and ozonolytic removal of the unwanted azidophenyl group to give the ketone **33** (Scheme 10). α-Bromination of the ketone was followed by displacement of the bromide with methyl thioglycolate in the presence of Hünig's base. The resulting compound was treated with ammonia in methanol to convert the ester into a



Scheme 10 Synthesis of shermilamine B.

carboxamide, with concomitant cleavage of the acetate, cyclization of which with boron trifluoride etherate gave the thiazinone **34**. The acetamide side chain was introduced by mesylation followed by reaction with the sodium salt of acetamide. The total synthesis of shermilamine B was completed by irradiation of the azide **35** at 110 °C in the presence of acetophenone as triplet sensitizer, followed by aromatization presumably by *in situ* oxidation to deliver the natural product (Scheme 10).

5.4 Thiaplidiaquinones A and B

Thiaplidiaquinones A and B were isolated from the Mediterranean ascidian *Aplidium conicum*, along with the aforementioned aplidinones and conicaquinones (Sections 3.3 and 4.1). The compounds contain unprecedented tetracyclic structures, featuring the 1,1-dioxo-1,4-thiazine-quinone unit and two geranyl side chains (Figure 17) (05JMC3410), although the central tricyclic quinone–chromenol fused system has been identified previously in two other natural products – microphyllaquinone and tecomaquinone. Weak optical rotations ($[\alpha]_D$~0) were determined for the thiaplidiaquinones, giving rise to the possibility that epimerization of the hydrogen at the chiral center occurred during the isolation and/or purification steps.

Both compounds display excellent cytotoxicities against a human leukemia cell line, with IC_{50} values of ~3 μM – comparable to doxorubicin. This antitumor activity is attributed to the quinone functionality, as quinones undergo redox cycling *via* the corresponding hydroquinone to generate reactive oxygen species such as superoxide. The compounds are yet to be synthesized.

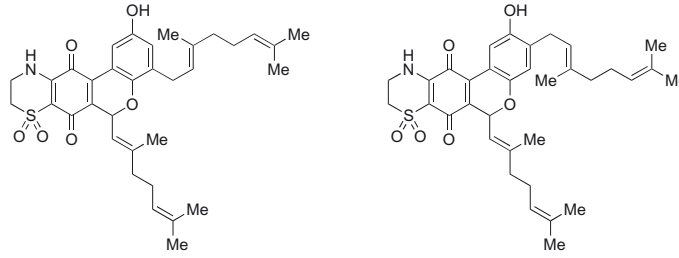


Figure 17 Structures of the thiaplidiaquinones.

6. CONCLUSIONS

This short review has highlighted the wide range of 1,4-thiazines that occur in Nature. The N,S-heterocycle appears in a number of guises, notably as simple monocyclic di- or tetrahydro derivatives with all possible oxidation levels at sulfur, as benzothiazinones, and as thiazine-*S*,*S*-dioxides fused to quinones. The review also shows that many of these interesting heterocyclic compounds are yet to succumb to synthesis, and we hope that the article will stimulate further work in this area.

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CHAPTER 3

Recent Advances in the Chemistry of 1,2,4-Triazines

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1. INTRODUCTION

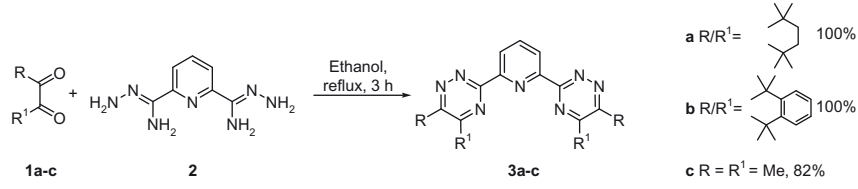
Interest in 1,2,4-triazines, as building blocks, reagents and chemical entities in their own right, is widespread and ongoing. Triazines are common pharmacophores, making them pervasive in both the pharmaceutical and agrochemical arenas. Furthermore, the electronic properties of the 1,2,4-triazine heteroaromatic ring impart distinct chemical properties that impact both the reactivity of, and synthetic approaches to, this ring system.

The authors of this review have long-standing involvement in heterocyclic chemistry (for instance, see 09CC3249, 09EJO2947, 09TL696, 09TL3318, 08OL2905, 08S3846, 07TL6556, 04OBC788, 04SL1628, 04TL3797, 03CC2286) and, in recent years, have become interested in the synthesis and applications of 1,2,4-triazines, *vide infra*. In this short review, we highlight recent advances made in the chemistry of 1,2,4-triazines, both by our group and many others over the last decade, from a purely synthetic chemistry standpoint. As such, we will not dwell on the physical organic concepts governing the processes unless directly pertinent. Furthermore, we focus on specific reactions of the 1,2,4-triazine system (or its derivatives) and will not attempt to review, for example, standard aromatic substitution reactions. Comprehensive reviews concerning 1,2,4-triazine chemistry are available (e.g., see 08PHC414, 05PHC337, 04PHC385, 04SOS357, 02AHC(82)261).

2. SYNTHESIS OF 1,2,4-TRIAZINES

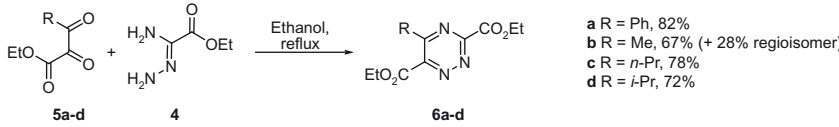
2.1 Condensations of 1,2-dicarbonyls and equivalents

The mainstay of 1,2,4-triazine synthesis is the double condensation of a 1,2-dicarbonyl unit with an amidrazone, an approach pioneered by Neunhoffer (see 96CHEC(6)507 and references therein) and continually exploited since. Recently, Hudson et al. (06NJC1171) have applied this methodology to the preparation of new bis(triazinyl)pyridines **3** for the extraction of americium(III) (Scheme 1). More recently, Yu et al. (07JOM

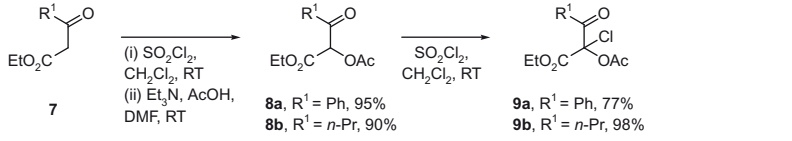


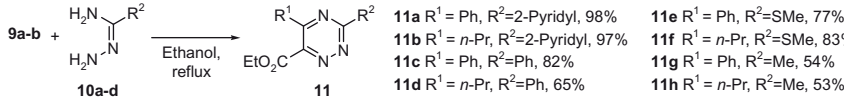
1a-c **2** **3a-c**

Scheme 1

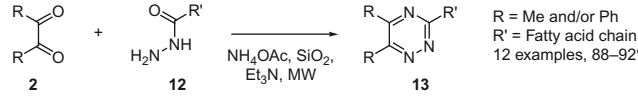


Scheme 2





Scheme 3



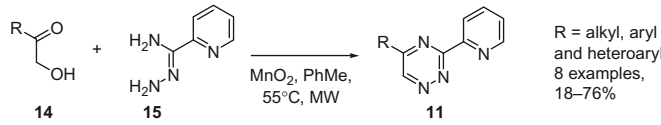
Scheme 4

(692)2306) have used a solvent-free version of this chemistry to prepare pseudo-N_3 ligands for ruthenium(II). The so-formed complexes were assessed for activity in the transfer hydrogenation of ketones.

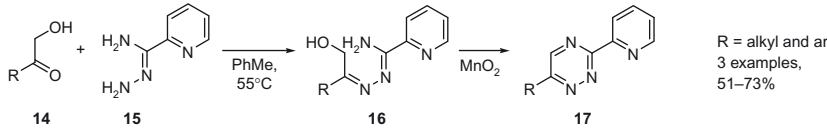
Stanforth's group has extended this concept to tricarbonyl substrates (02TL6015), allowing the synthesis of carboxy-substituted 1,2,4-triazines **6** (Scheme 2).

The same group then developed an analogous methodology, which allows the use of α,β-diketo-ester equivalents in the preparation of 1,2,4-triazines (05TL6111) (Scheme 3), presumably *via* an intermediate tricarbonyl species.

Recently, Rauf et al. (07ARK(xvi)137) have developed a microwave-mediated, solvent-free variant of the Neunhoffer chemistry that allows the preparation of 3,5,6-trisubstituted-1,2,4-triazines **13** from 1,2-dicarbonyls **2** and fatty acid hydrazides **12**, rather than amidrazones (Scheme 4). In a similar microwave-mediated approach, Nongkhlaw's group utilises 1,2-dicarbonyls, amides and hydrazine to construct 1,2,4-triazines (08ARK(xv)79).



Scheme 5



Scheme 6

2.2 Oxidative approaches

When the Neunhoffer double-condensation approach is applied to α-ketoaldehydes, the so-formed 3,5-disubstituted-1,2,4-triazines are often produced with excellent regioselectivity. However, α-ketoaldehydes are notoriously difficult to handle due to their high reactivity (85JOC2198). To circumvent these issues, the Taylor group (06TL3865) has developed methodology to allow the utilisation of α-hydroxyketones **14** in a one-pot tandem oxidation process (TOP), in which the α-ketoaldehyde in generated and trapped *in situ* (Scheme 5).

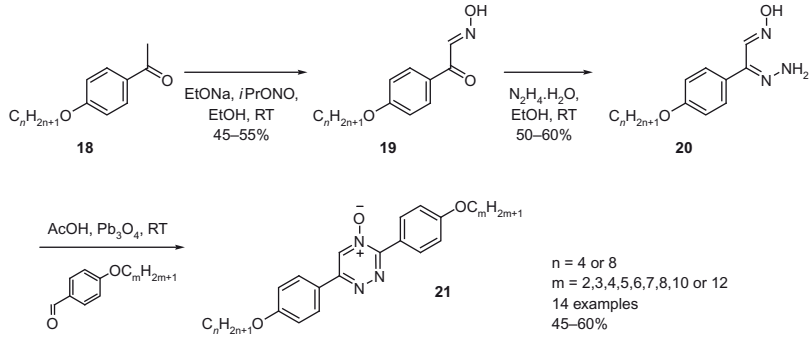
Despite the utility of Neunhoffer's double-condensation approach, and the modern variants, it remains difficult to access 3,6-disubstituted-1,2,4-triazines in a regiospecific manner. The need for viable technologies to accomplish this goal has, in recent years, led to the development of several complementary methodologies.

The Taylor group has extended its TOP-based methodology (06TL3865) to allow synthesis of the corresponding 3,6-disubstituted-1,2,4-triazines **17**, *via* intermediate condensation product **16** (Scheme 6).

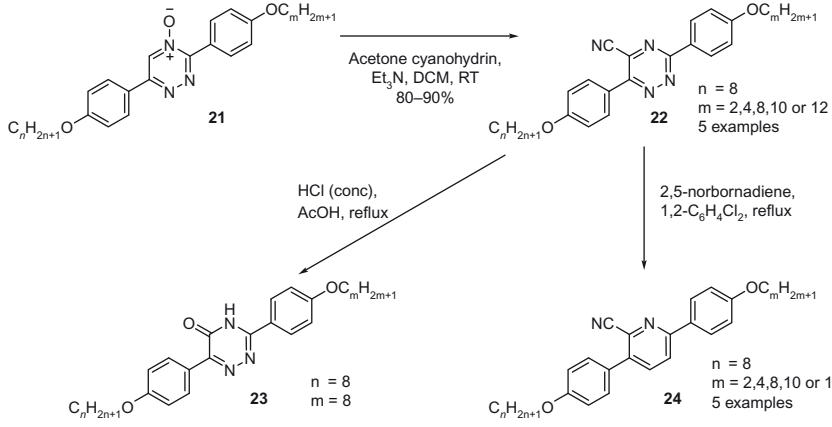
2.3 1,2,4-Triazine-*N*-oxides and their derivitisation

Kozhevnikov and co-workers (08JMC1703, 07CC3826) have recently developed a synthesis of 3,6-disubstituted-1,2,4-triazine-4-oxides **21** in a step-wise approach from an acetophenone **18** and an aldehyde (Scheme 7).

The triazine-4-oxides **21** can readily be converted into the corresponding 5-cyanotriazines **22** and, subsequently, to the 1,2,4-triazine-5(2*H*)-ones **23** or pyridines **24** (Scheme 8). In this particular report, the so-formed 1,2,4-triazines and 1,2,4-triazine-4-oxides are evaluated as new heterocyclic liquid crystals (08JMC1703).



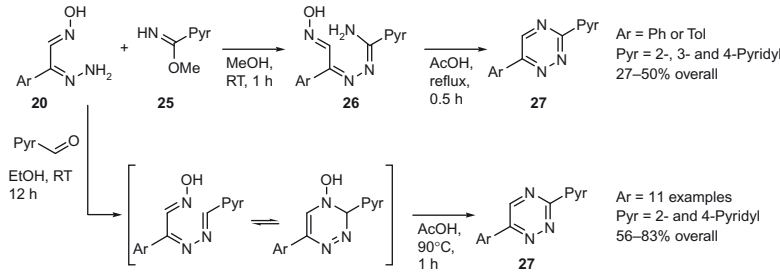
Scheme 7



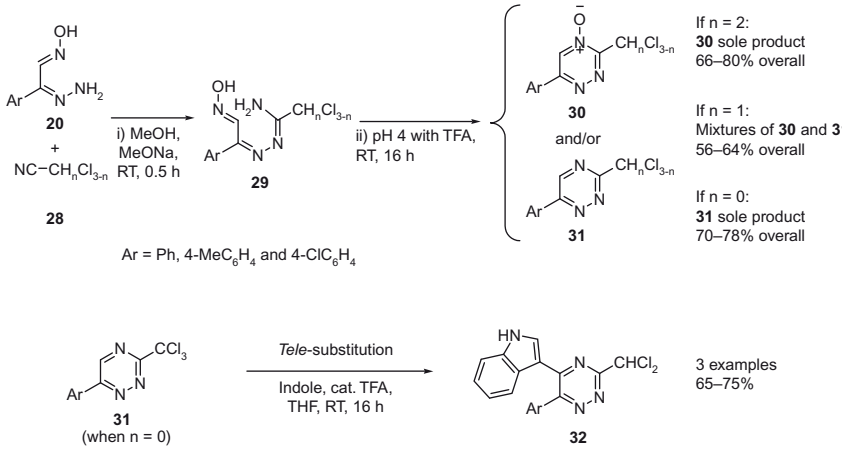
Scheme 8

The Kozhevnikov group (08T8963) has utilised hydrazones of type **20** in a direct synthesis of 3,6-disubstituted-1,2,4-triazines **27** from methoxyimidates **25** (Scheme 9). This group has also extended the scope of the condensation of hydrazones **20** with aldehydes to allow direct access to 3,6-disubstituted-1,2,4-triazines **27** (Scheme 9), rather than the 1,2,4-triazine-4-oxides **21** (as shown in Scheme 7), though this is limited to 2- and 4-pyridinecarboxaldehydes (or related benzopyridines).

Finally, the Kozhevnikov group (04IZV1243) has exploited hydrazone **20** in a divergent approach to polychloromethyl-1,2,4-triazines **31** and their 4-oxides **30** by reaction with polychloroacetonitriles **28** (Scheme 10). In this methodology, the degree of chlorination of the acetonitrile dictates the outcome of the reaction. Furthermore, in an interesting example of 1,2,4-triazine functionalisation, the so-formed 3-trichloromethyl-1,2,4-triazines



Scheme 9



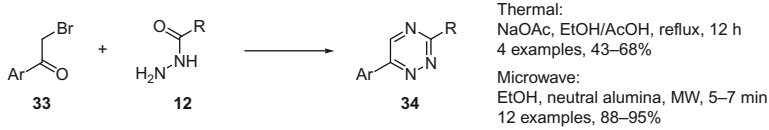
Scheme 10

31(*n*=0) are derivitised by *tele*-substitution with a variety of C-nucleophiles to furnish fully substituted 1,2,4-triazines of type **32** (indole is shown in Scheme 10 as an illustrative example, although several electron-rich aromatics have been investigated).

2.4 Miscellaneous approaches

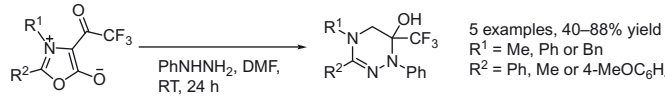
Another approach to the synthesis of 1,2,4-triazines that has seen some utilisation in recent years is the reaction of two equivalents of acyl hydrazone **12** with an α-haloketone **33** (Scheme 11). Both thermal (09IC4179, 01SC1639) and microwave-mediated (01SC1639) variants of this methodology have been exploited.

Kawase and Koiwai have developed an unusual ring-transformation methodology for the synthesis of trifluoromethyl-substituted 1,2,4-triazine derivatives (08CPB433). Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates



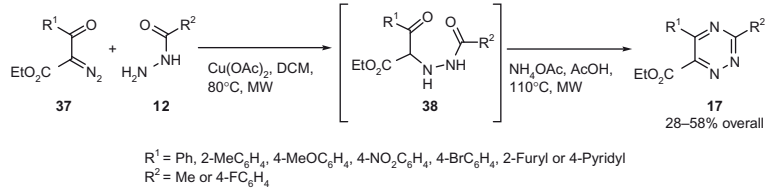
33 12 34

Scheme 11



35 36

Scheme 12



37 12 38 17

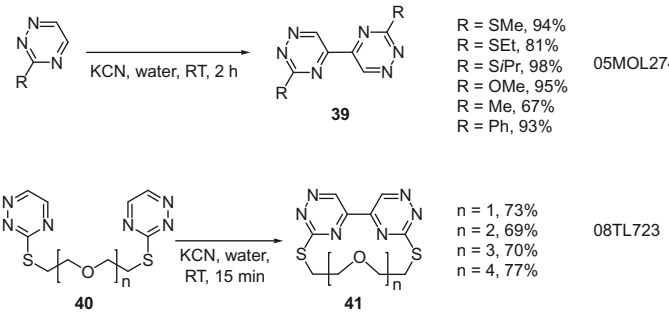
Scheme 13

35 are reacted with phenylhydrazine to give 1,4,5,6-tetrahydro-1,2,4-triazin-6-ols **36** (Scheme 12), 3-hydroxypyrazoles or pyrazolones depending on the solvent.

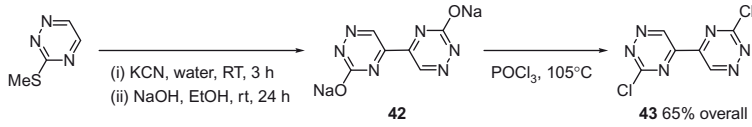
The most recent development in the synthesis of 1,2,4-triazines has been made by the Moody group (09OL3686). In this work, hydrazides **12** are reacted with copper carbenes derived from the corresponding α-diazo-β-ketoesters **37**. Condensation of intermediate **38** with ammonium acetate furnishes the trisubstituted-1,2,4-triazines **17** (Scheme 13).

3. FUNCTIONALISATION OF THE 1,2,4-TRIAZINE HETEROAROMATIC RING

1,2,4-Triazines are very π-deficient heterocycles and, consequently, every carbon atom in the ring is susceptible to nucleophilic attack. The selectivities of such reactions are modulated by the substitution around the ring. In this section, we seek to summarise some of the recent advances in the functionalisation of the 1,2,4-triazine scaffold.



Scheme 14



Scheme 15

3.1 Dimerisation

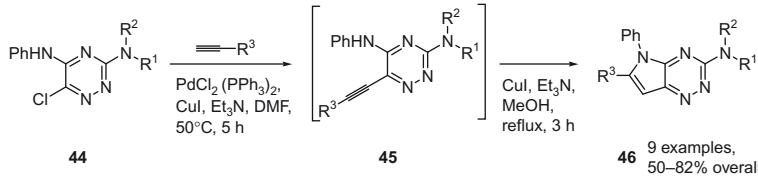
In an analogous manner to quinazolines (86H(24)1243), 1,2,4-triazines can be readily dimerised in the presence of KCN to produce bi-1,2,4-triazines. This nucleophilic addition–elimination transformation can be carried out in both an intermolecular (08TL719, 07EJO3414, 05MOL274) and an intramolecular (08TL723) fashion (Scheme 14).

This approach to bi-1,2,4-triazines has been extended by Wolińska to include a one-pot oxidation-hydrolysis sequence (09H(78)623), yielding the corresponding bi-1,2,4-triazinolate **42** (Scheme 15). This, in turn, can easily be converted into chloride **43**, itself typically susceptible to displacement by primary and secondary amines.

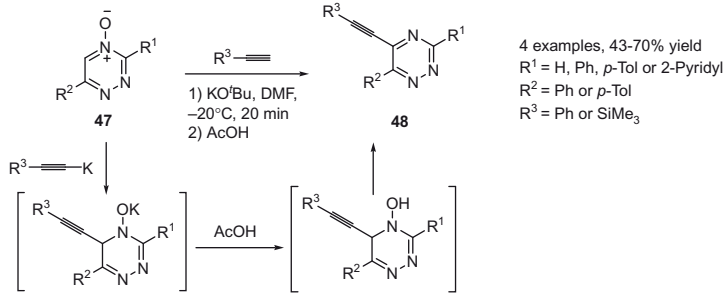
3.2 Substitution chemistry of 1,2,4-triazines

Recently, Nyffenegger et al. (07TL5069) have utilised the Sonogashira reaction for the functionalisation of 5-chloro-1,2,4-triazines **44** to make precursors of type **45** in the synthesis of 5*H*-pyrrolo-[2,3-*e*]-1,2,4-triazines **46** (Scheme 16). The most efficacious conditions were found to be a two-step, one-pot telescoped reaction.

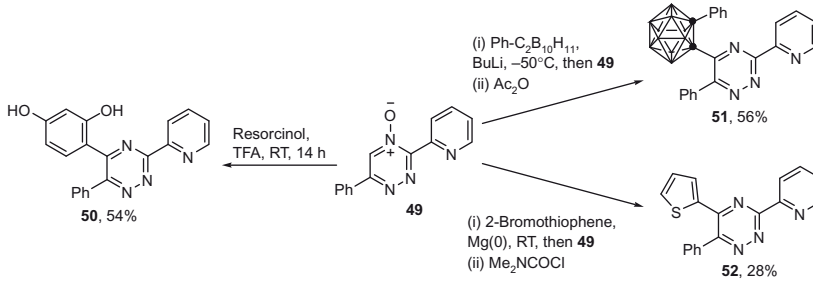
Acetylenic 1,2,4-triazines can also be produced *via* direct introduction of acetylenes by methodology based on the aromatic nucleophilic



Scheme 16



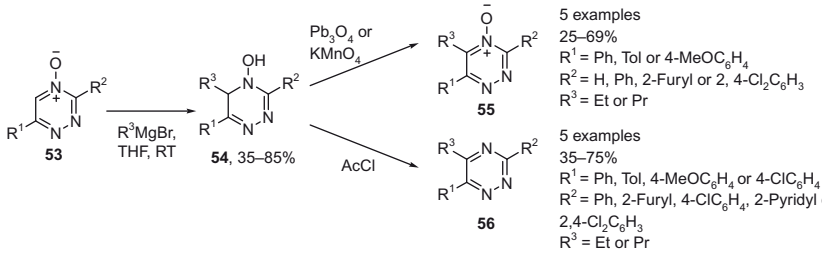
Scheme 17



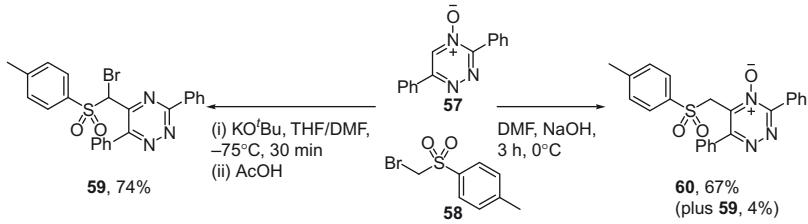
Scheme 18

substitution of hydrogen, or S_NH (09TL1444). Prokorov et al. utilise the triazine *N*-oxides **47** to produce alkyne-elaborated 1,2,4-triazines **48** (Scheme 17).

The S_NH reaction of *C*-nucleophiles with 1,2,4-triazine-4-oxides has, in recent years, been extended to many other nucleophiles. For example, Kozhevnikov et al. (06TL869) have used the methodology to introduce aromatic- **50**, heteroaromatic- **52** and carborane-substituted **51** triazines (Scheme 18). As discussed in Section 2.3 (Scheme 8) acetone cyanohydrin can be used to introduce a nitrile moiety by S_NH (08JMC1703, 05IZV2122).



Scheme 19



Scheme 20

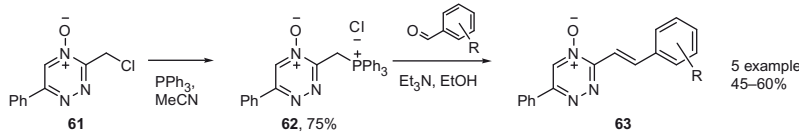
The *tele*-substitution reactions of trichloromethyl-1,2,4-triazine-4-oxides (04IZV1243) with indole have already been discussed in Section 2.3 (see Scheme 10).

In addition to the examples cited above, in which 1,2,4-triazine-4-oxides have been converted into 4-*C*-substituted-1,2,4-triazines, there have been recent reports in which the *N*-oxide functionality can be retained or eliminated depending on the conditions. Rusinov's group (03PJC1157) has shown that Grignard reagents can be reacted with triazine-4-oxides of type **53** to yield either the substituted triazine-4-oxide **55** or the parent triazine **56**, *via* the 4-hydroxy-4,5-dihydro-1,2,4-triazines **54** (Scheme 19).

Kozhevnikov et al. (02EJO1412) have investigated the vicarious nucleophilic substitution reactions of 1,2,4-triazine-4-oxides **53**. They have shown that, although mixtures are often formed, by tuning the conditions the reaction can be biased to favour either the deoxygenated (**59**) or dehalogenated product (**60**). For a representative example, see Scheme 20.

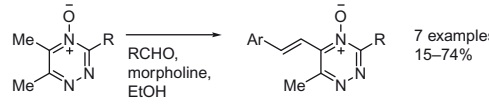
3.3 Substituent activation

The 4-oxo functionality can also serve to activate alkyl groups in the 5-position and, indeed, this effect has been exploited. In the first example (05IZV2122), the corresponding Wittig reagents **62** were prepared from chlorides **61** and shown to deliver the expected alkene products **63** (Scheme 21).



61 62, 75% 63

Scheme 21



64 65

Scheme 22

Secondly, 5-methyl-1,2,4-triazine-4-oxides **64** have been shown to undergo Mannich-type reactions (04MI1) (Scheme 22), although the yields are poor in some cases. Two examples of the analogous reaction with a 1,2,4-triazine-1,4-dioxide are also discussed in this report, with yields of 62% and 80%.

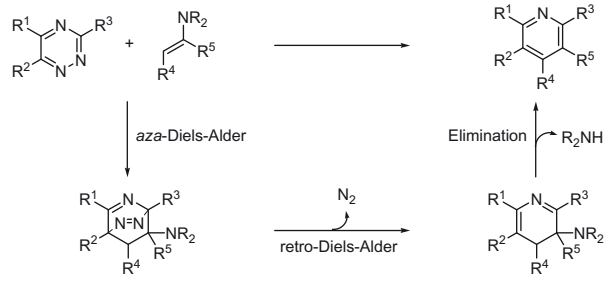
4. INVERSE ELECTRON DEMAND *AZA*-DIELS–ALDER REACTIONS OF 1,2,4-TRIAZINES

4.1 With enamines

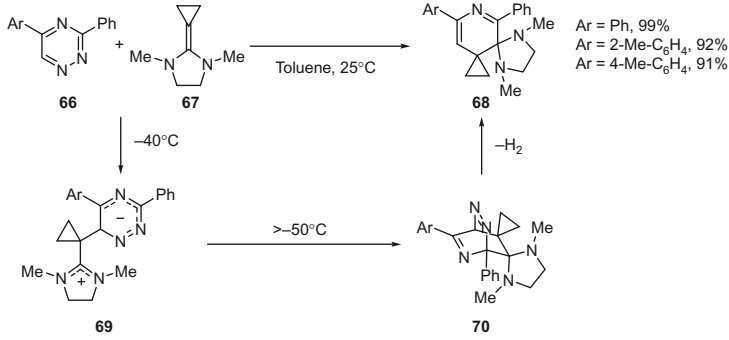
Probably the most valuable transformation of the 1,2,4-triazine ring system is the inverse electron demand *aza*-Diels–Alder reaction with enamines to produce substituted pyridines (for primary references, see 96CHEC(6)507, 89JOC1249, 85JA5745, 83T2869, 82JOC895, 81JOC2179). A general mechanism for the transformation is given in Scheme 23. This reactivity is partly explained by the reduced aromaticity of the triazine ring compared to benzene, pyridine and the diazines (07STC593). The regioselectivity of the initial *aza*-Diels–Alder step is governed by the substitution on the 1,2,4-triazine. In general, the mode shown in Scheme 23 dominates if R^3 is sp^2 hybridised (96CHEC(6)507, 87MI1).

Though for synthetic purposes the reaction can be considered a concerted process, Zipse and co-workers (05HCA1491) have carried out studies elucidating the step-wise nature of the mechanism proceeding *via* the intermediary zwitterion **69** (Scheme 24). A similar study has also been carried out for 1,3,5-triazines (05JOC998), once again highlighting the step-wise mechanism.

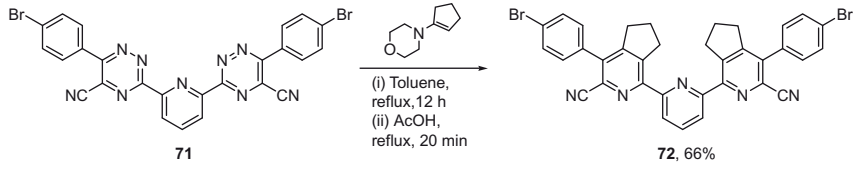
Given the pedigree of the reaction of 1,2,4-triazines with enamines, this review will highlight only a few recent uses to exemplify the



Scheme 23



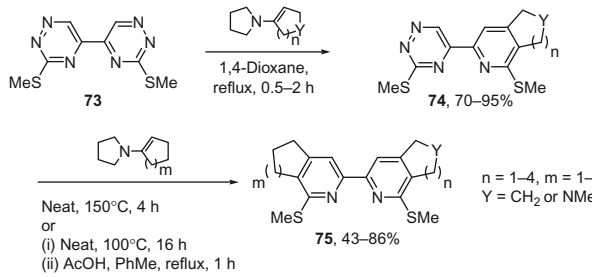
Scheme 24



Scheme 25

chemistry. Kozhevnikov et al. (03S2400) have employed such chemistry in the preparation of terpyridine ligands such as **72** (Scheme 25). In this instance, the reaction is carried out on a scaffold containing two triazine moieties.

Branowska and co-workers have also utilised scaffolds containing two triazine units (5,5′-bi-1,2,4-triazines **73**) in the *aza*-Diels–Alder chemistry (05MOL265, 03S2096). However, in these examples, the triazines are reacted sequentially to produce differentiated bipyridines of type **75** *via* intermediate **74** (Scheme 26). Synthesis of analogues of **75**



Scheme 26

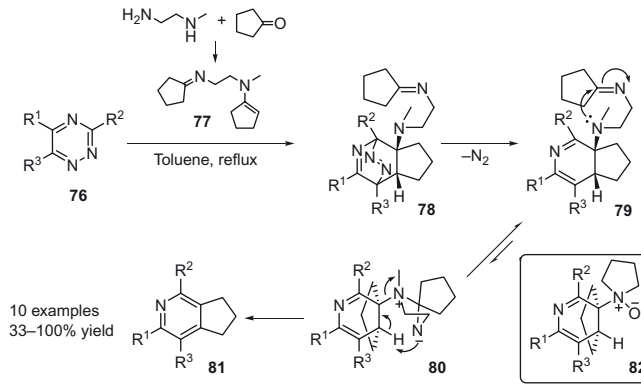
containing one annulated and one non-annulated pyridine *via* similar methodology has also been reported (09H(78)457, 03S2096). The non-annulated pyridine is derived from the 1,2,4-triazine moiety with vinyl imidazole.

Other recent examples of this *aza*-Diels–Alder methodology include Stanforth's syntheses of 2,2′-bipyridines (09T975) and 2,2′:6′,2″-terpyridines (09T1115), and Kozhevnikov's syntheses of highly functionalised and tuned ligands for chelation of platinum (09IC4179, 08AGE6286, 08TL4096) and copper (08JOM(693)1886).

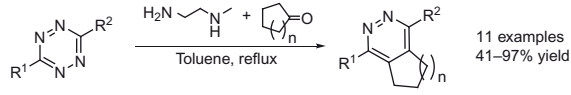
Despite its obvious utility, the enamine-mediated *aza*-Diels–Alder methodology can suffer from one principal limitation, that being the unusual stability of the intermediate dihydropyridines (88JOC5175, 82JOC895). This is due to the synperiplanar configuration of the proton and amine. As can be seen if one studies the examples of the methodology cited in Section 4.1, this often necessitates (A) the use of forcing conditions (high temperature) to effect the aromatisation in 'one-pot' (e.g. 08TL4096, 03S2096); (B) facilitation of the aromatisation *via* a discrete elimination step mediated by acetic acid (e.g. 09T975, 03S2096) or (C) oxidation of the tertiary amine to effect Cope elimination (88JOC5175).

In an effort to address this issue, Raw and Taylor have developed a tethered imine-enamine (TIE) methodology for the synthesis of highly substituted pyridines from 1,2,4-triazines **76** (04CC508, 05JOC10086). The rationale is the *in situ* formation of a zwitterion **80**, which, it is postulated, mimics the *N*-oxide **82** intermediate of the Cope elimination (Scheme 27). Alternatively, the internal base may promote epimerisation and so facilitate elimination through the antiperiplanar configuration. The tethered imine-enamine species (e.g. **77**) is produced from *N*-methylethylenediamine and the ketone *in situ* and the reaction proceeds under mild conditions to furnish the pyridines **81** directly.

The application of this TIE methodology has also been extended to the conversion of 1,2,4,5-tetrazines into the corresponding pyridazines (07ARK(xi)37) (Scheme 28).



Scheme 27

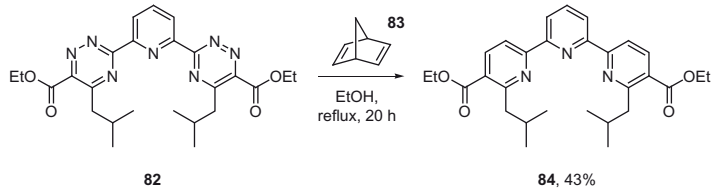


Scheme 28

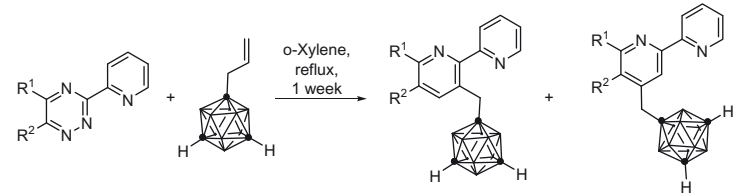
The Taylor group has continued to develop improved methodologies for the conversion of 1,2,4-triazines into polysubstituted pyridines. One variant is a solvent-free, microwave-mediated reaction in which pyrrolidine and the requisite ketone and 1,2,4-triazine are reacted to yield the desired pyridines in high yield (05JOC10086, 23 examples). In a complementary thermal variant, 1,2,4-triazines are reacted with pyrrolidine and the carbonyl component in toluene in the presence of silica, which once again furnishes the pyridine in a one-pot process (07SL2217, 9 examples). Again, this methodology has also been successfully applied to the transformation of 1,2,4,5-tetrazines to the pyridazines (07SL2217, 3 examples).

4.2 With alkenes

In addition to enamines, several other classes of electron-rich dienophile have been exploited in *aza*-Diels–Alder reactions with 1,2,4-triazines. Most common is norbornadiene **83**, which, *via* an *aza*-Diels–Alder/*retro*-Diels–Alder (eliminating nitrogen)/*retro*-Diels–Alder (eliminating cyclopentadiene) sequence, converts the 1,2,4-triazine into the corresponding pyridine with no additional functionality. This is an established methodology, and continues to be used to good effect today (for recent applications, see 09T975, 08TL719, 08TL4720, 07TL6974). Stanforth's



Scheme 29



Scheme 30

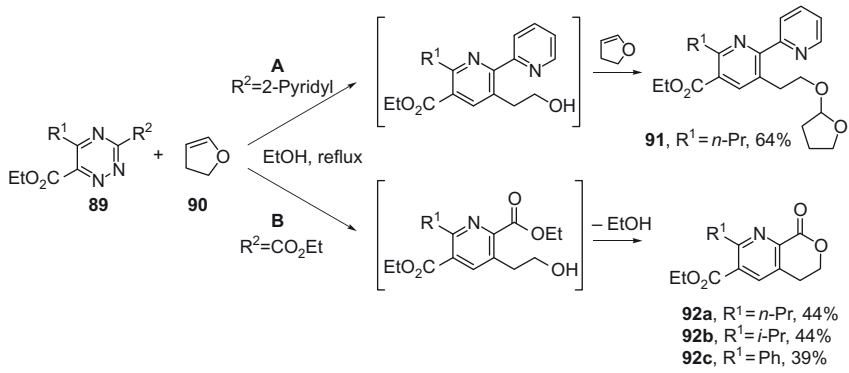
synthesis of 2,2′:6′, 2″-terpyridine **84** from bis-1,2,4-triazine **82** exemplifies the transformation (09T1115) (Scheme 29).

The strain imparted on the C═C double bonds in norbornadiene **83** accounts for its reactivity in *aza*-Diels–Alder chemistry. In general, alkenes without electron-donating groups react sluggishly or not at all. In the light of this, Prokhorov's synthesis of carborane-bearing pyridines from 9-allyl-1,7-dicarbadodecaborane **86** (08TL3785) is particularly noteworthy, despite the use of high temperatures and long reaction times (Scheme 30). It should be noted that the lack of electronic bias in the dienophile results in products **87**/**88** as a 1:1 mixture of regioisomers.

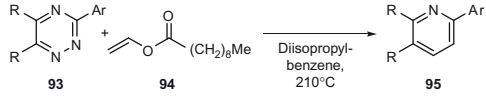
4.3 With enol ethers

Like enamines, enol ethers are sufficiently electron rich to undergo *aza*-Diels–Alder chemistry with high efficiency under mild conditions. For example, 2,3-dihydrofuran **90** reacts with triazines **89** to give pyridines with pendant protected alcohols **91** (09T975) (Scheme 31-A) or pyridines bearing annulated lactones **92** (04T8893) (Scheme 31-B) as the ultimate products, depending on the substitution pattern of the 1,2,4-triazine **89**.

In a search for more economic, less toxic alternatives to norbornadiene **83**, Shintou et al. (05CL836) have explored the use of vinyl alkanoates to carry out the analogous transformations of triazines **94** in



Scheme 31



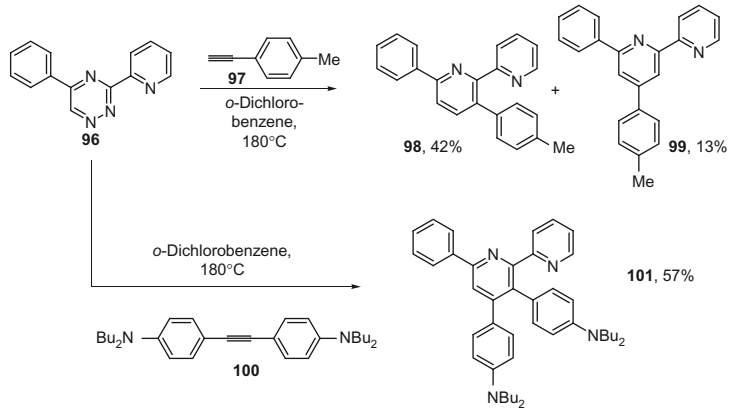
Ar = 3-Pyridyl, R=H, 90%
Ar = 2-Pyridyl, R=H, 93%
Ar = 2-Pyrimidyl, R=H, 89%
Ar = 5-Me-Pyrid-3-yl, R=H, 89%
Ar = 2-Pyridazinyl, R=Me, 91%

Scheme 32

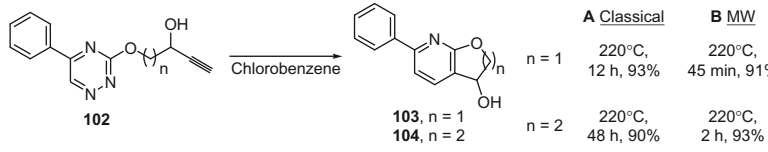
an industrial setting (Scheme 32). Several vinyl alkanoates were screened, but for the reasons of boiling point and unit cost, vinyl decanoate **94** was deemed most suitable. Although the reduction in electron density on the dienophile requires elevated reaction temperatures to achieve suitable reaction times, the pyridines **95** are returned in good yields and purity (in all cases, 98.9–99.5 area% by HPLC).

4.4 With alkynes

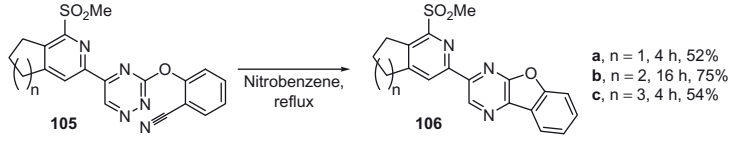
The use of alkynes in the *aza*-Diels–Alder reaction of 1,2,4-triazines has also been explored in the recent years. Ziessel's group has employed both mono- (07TL8069, 07JOC10181) and disubstituted (07SL3027, 07JOC10181) alkynes, **97** and **100**, respectively, in such chemistry for the synthesis of tri- and tetra-arylated bipyridine ligands (e.g. **98**, **99** and **101**). However, as with non-activated alkenes, the reactions require high temperature to achieve reasonable rates and conversions. Once again, the lack of strong electronic bias in mono-arylethyne dienophiles results in products being produced as regioisomeric mixtures. The two reaction variants are exemplified in Scheme 33.



Scheme 33



Scheme 34



Scheme 35

Work by Suzenet, Guillaumet and co-workers (09EJO3619, 07T8286) has shown that tethering the alkyne to the 1,2,4-triazine (e.g. **102**) does little to improve its reactivity in the *aza*-Diels–Alder reaction under classical thermal heating (Scheme 34-A). Branowska (04T6021) has also made similar observation and has developed microwave-mediated conditions to allow this type of intramolecular reaction to be performed more efficiently (Scheme 34-B). This microwave-mediated technology has been applied to a range of substrates (23 examples cited, of varying substitution patterns and chain lengths).

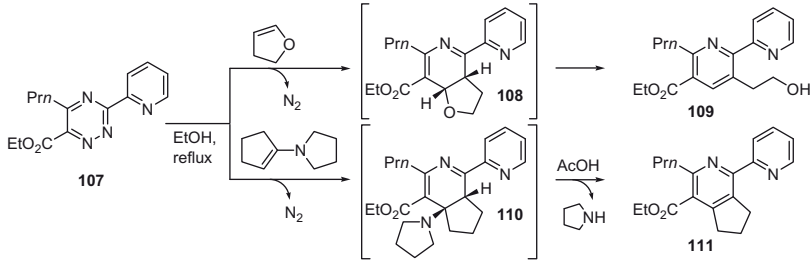
It should be noted that such aggressive thermal heating conditions also allow the use of otherwise non-reactive dienophiles, for example nitriles (04T6021) (Scheme 35), resulting in the synthesis of annulated piperazines **106** from the corresponding 1,2,4-triazines **105**.

5. CASCADE REACTIONS OF 1,2,4-TRIAZINES

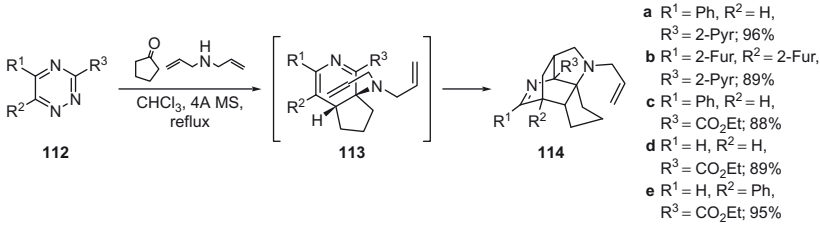
5.1 From 1,2,4-Triazines to polycyclic ring systems

All the *aza*-Diels–Alder transformations of the 1,2,4-triazine ring discussed in Sections 4.1, 4.2, 4.3 and 4.4 result in an aromatic product, usually the corresponding pyridine, as a consequence of aromatisation by elimination from the dihydropyridine precursor. An illustrative example is the conversion of triazine **107** into pyridines **109** and **111**, *via* dihydropyridines **108** and **110** (09T975) (Scheme 36).

However, the *s-cis*-2-azabutadiene moiety extant in dihydropyridines, such as **108** and **110**, is also a reactive partner in *aza*-Diels–Alder chemistry (83T2869, 93AHC(57)1, 87MI1). Raw and Taylor, together with co-workers, have harnessed this reactivity in the development of cascade reactions of 1,2,4-trazines for the production of complex nitrogen-containing polycyclic ring systems (04JA12260, 07T6004). In this methodology, the dihydropyridine **113**, produced *via* the expected *aza*-Diels–Alder/*retro*-Diels–Alder sequence, is trapped with a tethered dienophile in a second *aza*-Diels–Alder reaction, producing the 7,11-diazatetracyclo [7.3.1.$0^{2,6}$.$0^{6,10}$]tridec-11-enes **114** in excellent isolated yields (Scheme 37).



Scheme 36

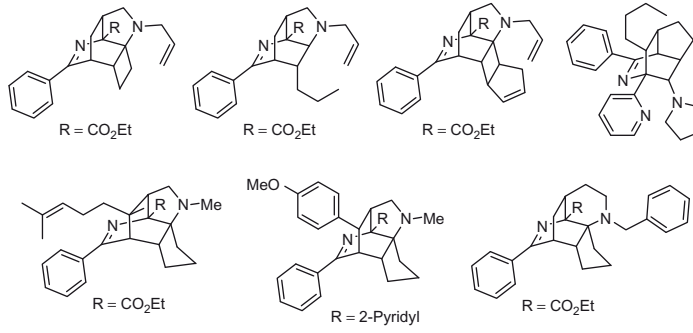


Scheme 37

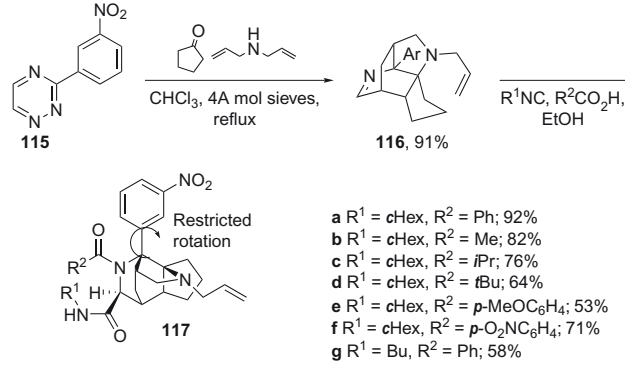
In this methodology, the molecular complexity dramatically increases from one ring (the 1,2,4-triazine **112**) to a tetracyclic skeleton containing six new stereogenic centres and four new carbon–carbon bonds!

In addition to the five examples illustrated in Scheme 37, showing differentiation only in the 1,2,4-triazine substrate **112**, the concept has been applied to a total of 21 examples. By varying the nature of the 1,2,4-triazine, tethered dienophile and ketonic partner, many structurally diverse tri-, tetra- and pentacyclic ring systems can be accessed, some of which are illustrated in Scheme 38.

The dramatic increase in molecular complexity and the opportunity for divergency offered by this methodology has attracted the attention of groups interested in diversity-oriented syntheses of bioactive compound libraries (08NPR719). Indeed, the Nelson group (09CEJ2185) has extended the cascade to incorporate a Joullié–Ugi reaction, allowing further diversification (Scheme 39).



Scheme 38



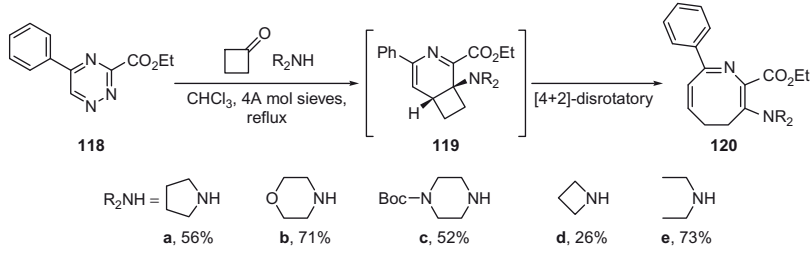
Scheme 39

The so-formed tetracyclic products **117a–g** are of particular note due to their unusual rotameric properties: the bridgehead aromatic group encounters significant steric barrier to rotation about the sp^2–sp^3 carbon–carbon bond, despite its lack of *ortho*-substituents. Indeed in some instances, the rotamers can be separated by low-temperature preparative HPLC! These are the first compounds in which such an effect has been noted.

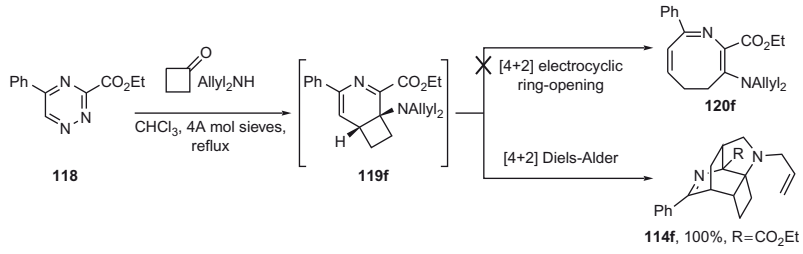
5.2 4,5-Dihydroazocines

Raw and Taylor (04TL8607) have also exploited the reactivity of the transient *s-cis*-2-azabutadiene moiety in a cascade process for the synthesis of 4,5-dihydroazocines (Scheme 40). In this sequence, the strained dihydropyridines **119**, formed from the reaction of **118** with an enamine derived from cyclobutanone and various secondary amines *in situ*, undergo disrotatory [4+2]-electrocyclic reaction to produce the trisubstituted-4,5-dihydroazocines **120**.

Interestingly, the electrocyclic ring opening of dihydropyridines **119** is apparently slower than the intramolecular *aza*-Diels–Alder reaction depicted in Scheme 35. So, when triazine **118** is reacted with the enamine derived from cyclobutanone and diallylamine *in situ*, the tetracycle **114f** is the sole product, isolated in quantitative yield (04TL8607) (Scheme 41).



Scheme 40



Scheme 41

6. USE OF 1,2,4-TRIAZINES IN TOTAL SYNTHESIS

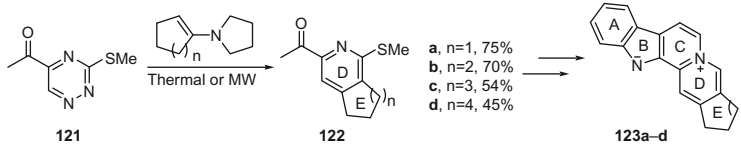
Although 1,2,4-triazines have been extensively utilised in the synthesis of ligands (e.g. 08TL4096, 07JOC10181, 07TL8069, 03S2096, 03S2400), liquid crystals (e.g. 08JMC1703, 08AGE6286) and cyclophanes (e.g. 09H(78)457, 08TL723), they have not often been exploited in natural product total synthesis.

6.1 Semipervirine

Lipińska has used the *aza*-Diels–Alder reaction of a 1,2,4-triazine **121** to construct the D/E-ring system **122b** of Semipervirine **123b** (06T5736, 05T8148). The divergency afforded by the methodology also allows the easy synthesis of analogues containing different E-rings **123a,c,d** (Scheme 42).

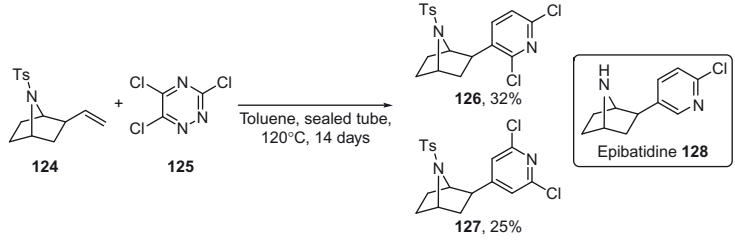
6.2 Epibatidine

Armstrong et al. (07JOC8019) investigated a synthetic approach to (±)-epibatidine **128** from 3,5,6-trichloro-1,2,4-triazine **124** (Scheme 43). However, the approach was abandoned due to the poor selectivity in the *aza*-Diels–Alder reaction and the anticipated difficulty in the selective removal of the extra chlorine from **127**. The authors did note the utility of this approach as a convenient means of varying the heteroaromatic portion of epibatidine in analogue synthesis.



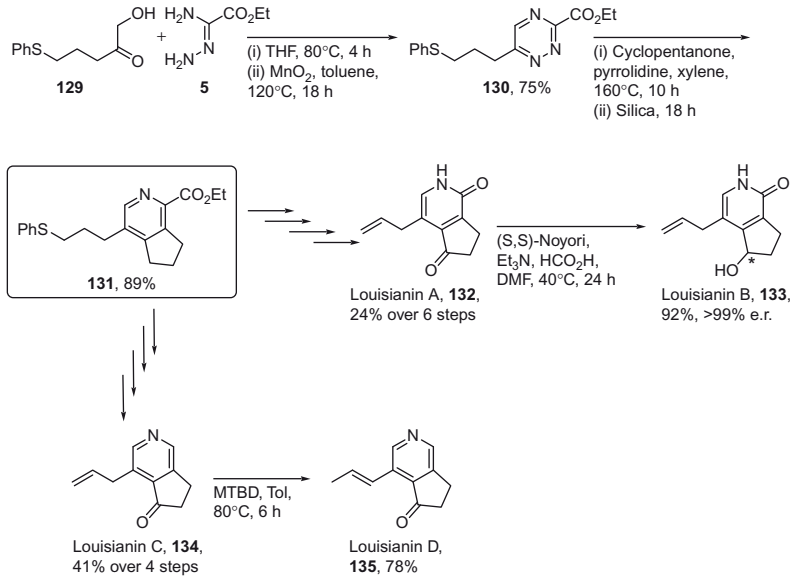
121 **122** **123a–d**

Scheme 42



124 **125**

Scheme 43



Scheme 44

6.3 Louisianins A–D

Finally, the Taylor group has exploited the *aza*-Diels–Alder reaction of 1,2,4-triazine **130** in the synthesis of the Louisianin family of alkaloids (08TL2865, 09JOC8343). The 3,6-disubstituted-1,2,4-triazine **130** is prepared regioselectively using TOP methodology (06TL3865) (Scheme 44), then converted into the key pyridine **131** using the improved methodology developed by the group for the *aza*-Diels–Alder reaction with enamines (07SL2217). This common pyridine intermediate **131** is then converted into the Louisianins: firstly, into Louisianin A **132** in six steps, from which stereocontrolled reduction furnishes essentially enantio-pure Louisianin B **133**; secondly, into Louisianin C **134** in four steps, from which simple isomerisation of the double bond furnishes Louisianin D **135**.

7. SUMMARY

The body of work summarised in this review shows that research into the chemistry of 1,2,4-triazines remains of great interest, given the pharmaceutical and agrochemical value of these compounds and their importance as synthetic building blocks. The recent developments reported herein cover new synthetic routes to 1,2,4-triazines, particularly regioselective procedures, and their utility in synthetic investigations. Of the various

transformations discussed, the use of substituted 1,2,4-triazines to prepare a range of valuable polysubstituted pyridines, bipyridines and terpyridines is perhaps the most useful. Recent applications of 1,2,4-triazines in reaction cascade methodology for the preparation of both 7,11-diazatetracyclo[7.3.1.$0^{2,6}$.$0^{6,10}$]tridec-11-enes (and related ring systems) and 4,5-dihydroazocines has also been covered.

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CHAPTER 4

Heteroaryl Radicals Review

Danilo Mirizzi[a], **Stephen T. Hilton**[b] and **Keith Jones**[a]

Contents

1. INTRODUCTION

This review covers the synthetic uses of heteroaryl σ-radicals in which the unpaired electron occupies an sp^2 hybrid orbital orthogonal to the π-system. These are generally derived from heteroaryl bromides or iodides under suitable conditions for radical generation and propagation. In 1985, Beckwith and Schiesser (85TL373) determined the rate constant for 5-*exo* cyclisation of the *ortho*-(but-3-enyl)phenyl radical as $3 \times 10^8\ s^{-1}$. This is some three orders of magnitude faster than the rate constant for the simple alkyl version of this reaction, the cyclisation of the 5-hexenyl radical to give the cyclopentylmethyl radical (85T3925). This clearly demonstrates the inherent reactivity of such aryl σ-radicals. Although there are no direct measurements available for heteroaryl systems, the

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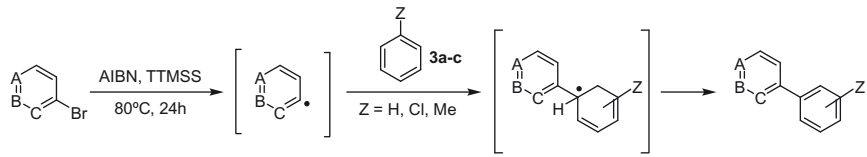
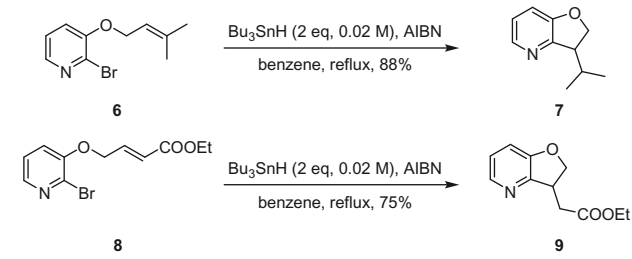
orthogonal nature of the unpaired electron and the π-system means that the phenyl radical reactivity should be reflected in the heteroaryl radical reactivity. Although a review has appeared on the use of aryl radicals in synthesis (99COC469), no review specifically covering heteroaryl radicals has appeared. There have been some reviews that have described the synthesis of heterocycles *via* radicals (00JCSP11), (97COS261); these may have touched upon but have not focused upon heteroaryl radicals as intermediates. Due to the plethora of substrates and range of reactions involving heteroaryl radicals, the following review is organised by the type of heteroaromatic radical involved.

2. PYRIDYL RADICALS

Among the class of heteroaromatic radicals, pyridyl radicals are the most widely studied. Some very early examples are available, but their synthetic applications are limited. Antoine reported the generation of a pyridyl radical (64CR4742), using ^{60}Co γ-rays, to give a polymer. Zoltewicz studied the reduction of pyridyl and some quinolyl and isoquinolyl radicals, starting from the respective halo derivative using sodium methoxide under both photochemical and thermal conditions (75JA5889), (83JOC4214). Ford studied the thermal decomposition of nicotinyl peroxide in some aromatic solvents (58JCS1294), with subsequent generation of the respective 3-aryl pyridine. Other authors have published work on the addition of pyridyl radicals to aromatic solvents. Ryang (72CC594), Seki (86H(24)799), Osborne (89TL3567) and Terashima (85CPB1009) performed the synthesis of 2-arylpyridines *via* photochemical generation of 2-pyridyl radicals from 2-iodopyridine and subsequent addition to substituted arenes. Yields increase as the substituent on the benzene ring become more electron donating, reflecting the electrophilic character of the pyridyl radical with *meta*-isomers as the major products. From a synthetically more useful point of view, Alvarez-Builla performed the same reaction (00OL3933), for 2-, 3- and 4-pyridyl radicals **2a–c**, using more commonly used radical conditions (04T6217) (Scheme 1).

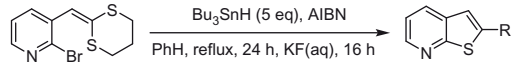


Scheme 1



6 **7** **8** **9**

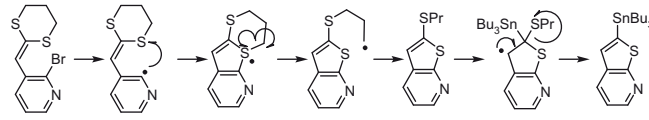
Scheme 2



10

11a, R = H
11b, R = $C_3H_6SSnBu_3$
11c, R = SC_3H_7

Proposed Mechanism:



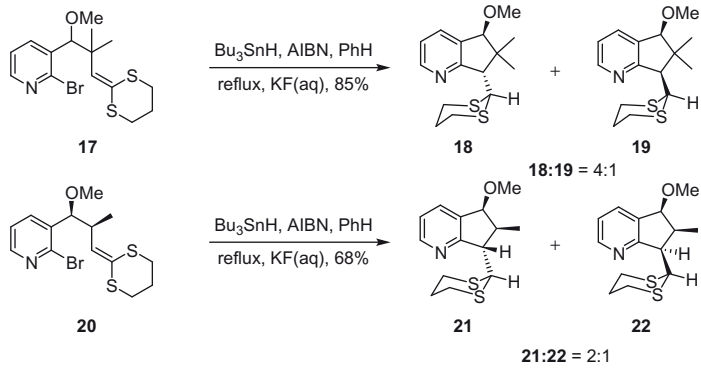
10 **12** **13** **14** **11c** **15** **16**

Scheme 3

The best results were obtained when two equivalents of both AIBN and TTMSS (slowly added) were used, implicating the involvement of the radical initiator in the rearomatisation (oxidation) step. Interestingly, use of Bu_3SnH, instead of TTMSS, gave very poor yields. With a growing interest in new methodology to create C–C bonds, an increasing number of syntheses employing pyridyl radicals are found in the literature. Snieckus described a successful addition–cyclisation to double bonds performed by a 2-pyridyl (and a 4-pyridyl, although no yield was reported) radical (85TL6001, 88BSF67) to give products **7** and **9** in good yield (Scheme 2).

As shown, 5-*exo*-trig cyclisation proceeds smoothly following Beckwith's conditions for the corresponding phenyl substrates (85T3925), demonstrating that pyridyl radicals undergo addition to unsaturated bonds in a similar fashion to phenyl radicals. In a very different type of reaction, Harrowven synthesised thieno(2,3-*b*)pyridines **11a–c** from ketenedithioacetals *via* the 2-pyridyl radical precursor **10** (95TL2861) (Scheme 3).

The proposed mechanism involves attack by the σ-radical onto the sulphur atom, giving rise to a cascade to obtain the final tin derivative **16**.

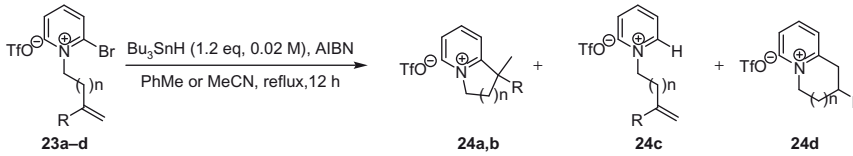


Scheme 4

Reduction product **11a** is prposed to be obtained during purification. In a preceding paper (93TL5653) **11b** (62%) and **11c** (12%) were obtained. From the same group, further studies on the 2-pyridyl radical have been reported and are outlined below where products **18**, **19**, **21** and **22** were obtained (94TL5301) (Scheme 4).

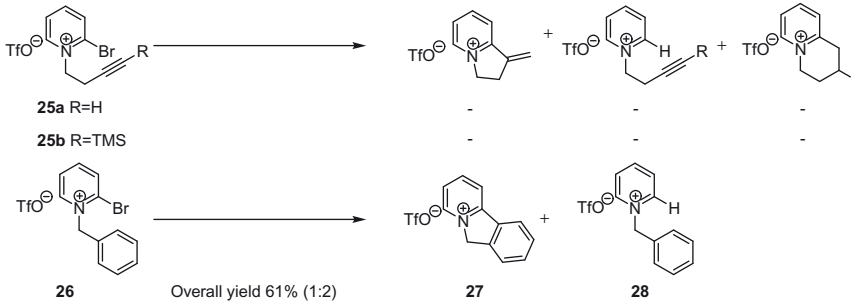
The simple expedient of the selection of an appropriate substrate, avoids the cascade observed in Scheme 3 and a more typical radical addition to the double bond is observed to give products **18**, **19**, **21** and **22** (Scheme 4). Jones published an example of addition of a 2-pyridinium radical from precursors **23a–d** to unsaturated bonds (97TL5383) (Scheme 5).

Use of toluene as solvent, gave a 65% yield of **24a** (entry 1), owing to the poor solubility of the pyridinium salt. Acetonitrile, however, increased the yield of **24a** to 74%, and resulted in exclusive 5-*exo* cyclisation. Note that the disfavoured 6-*endo* cyclisation or possible rearrangement of the cyclopentylmethyl radical generated by addition of the 2-pyridinium radical to the double bond does not occur. Extension of the alkyl chain by one carbon gave rise to 6-*exo*-cyclisation product **24b**, while no trace of the 7-*endo* product was observed. Further extension of the chain gave reduced product **24c** (entry 3). An increase in steric bulk around the double bond (entry 4), resulted in a mixture of **24d**, where the 6-*endo* product was favoured, in accordance with Beckwith's results (85T3925). Any attempt at cyclisation onto an alkyne triple bond from precursors **25a,b** resulted in inseparable products, with little or no evidence of cyclisation. Cyclisation–rearomatisation to an aromatic ring from **26**, gave a moderate yield of the expected cyclised product **27**. This final result could be explained by the use of a substoichiometric amount of initiator, which has since been shown to be an important factor in the rearomatisation (oxidation) step. Similar work using alkyl pyridinium salts has been reported by Park (97JA10677) (Scheme 6).

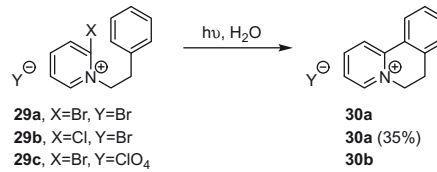


23a–d 24a,b 24c 24d

Entry	Starting material	*exo*-product	Reduction	*endo*-product
1	**23a** R=H, n=1	**24a** (74%)	-	-
2	**23b** R=H, n=2	**24b** (53%)	-	-
3	**23c** R=H, n=3	-	**24c** (47%)	-
4	**23d** R=CH_3, n=1	**24d** (17%)	-	**24d** (59%)



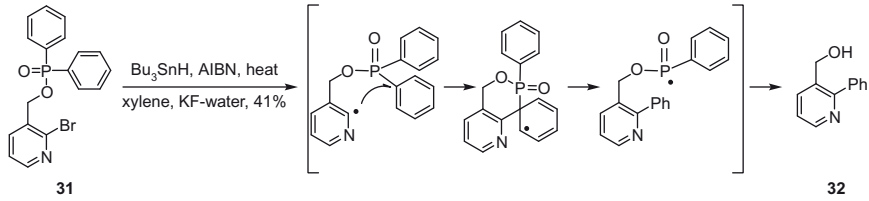
Scheme 5



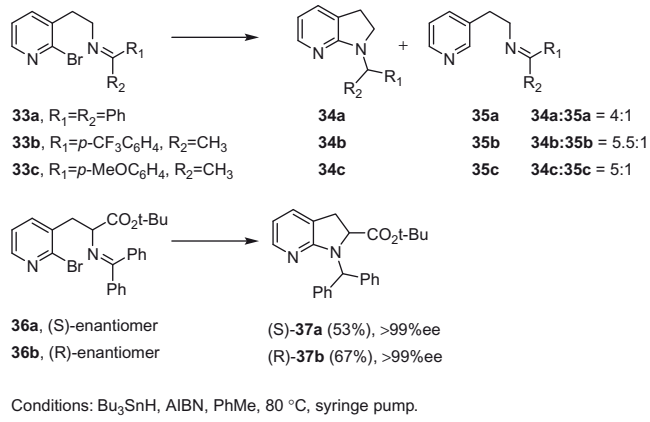
Scheme 6

Photochemical generation of 2-pyridinium radicals facilitated intramolecular cyclisation–rearomatisation onto the benzene ring to give tricyclic **30** (Scheme 6) (97JA10677). Clive highlighted an example of pyridyl radicals that differ from typical radical addition to unsaturated bonds (Scheme 7) (00TL1315, 2001JOC6083). The known *ipso*-substitution found for aryl sulphonates (91CC877, 1997TL141) is here extended to phosphinate **31**, resulting in biaryl **32** (Scheme 7).

Johnston successfully cyclised 2-pyridyl radicals onto a C═N bond (01OL1009, 03JA163, 05S330), with regioselective addition to the imine



Scheme 7

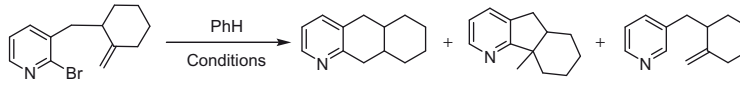


Scheme 8

nitrogen, in a 5-*exo* fashion to produce cyclised products **34a–c** from precursors **33a–c** (Scheme 8).

In the first example, the electronic requirements were investigated with similar outcomes. The final yields of cyclised **34a–c** were calculated over two steps, so radical precursors **33a–c** were not isolated. However, the cyclised to reduced ratio was in favour of the former. In the second example, an asymmetric synthesis of azaindolines **37a** and **37b** was successfully achieved by radical cyclisation of enantiomerically pure **36a** and **36b**. The neutral conditions used preserve the stereogenic centre, demonstrating the potential of this approach. Banerjee (02JCS(P1)1769) reported a study of an intramolecular radical addition of a 2-pyridyl radical from **38** onto a double bond to produce the tricyclic products **39–41** (Scheme 9).

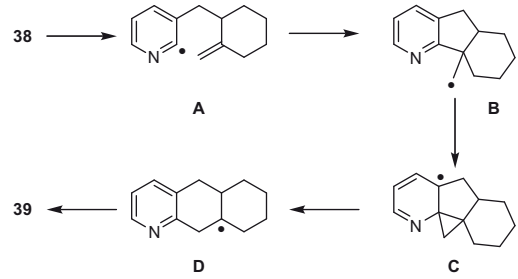
The ratio of the three possible products **39**, **40** and **41**, is highly influenced by the concentration of Bu_3SnH. Note that in this case, the 6-*endo* product is predominant over the 5-*exo*, probably owing to the rearrangement of the generated alkyl radical **A** *via* cyclopropyl intermediate **C**. In a later paper (05S3067), the same group carried out



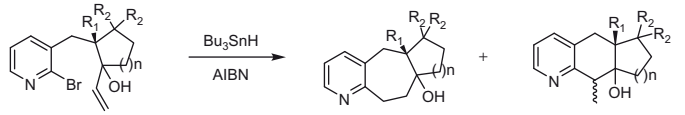
38 39 40 41

Conditions	39	40	41
Bu_3SnH (0.1 M), AIBN, reflux	12%	4%	84%
Bu_3SnH (0.01 M), AIBN, reflux	67%	8%	25%
Bu_3SnH (0.002 M), AIBN, reflux	100%	–	–
Bu_3SnH (0.1 M), Et_3B, 25°C	16%	2%	82%
Bu_3SnH (0.003 M), Et_3B, reflux	61%	1%	38%

Proposed mechanism:



Scheme 9



42, R_1=Me, R_2=H, n=2, *cis*-isomer
45, R_1=H, R_2=Me, n=2, *trans*-isomer
48, R_1=R_2=H, n=1, *trans*-isomer

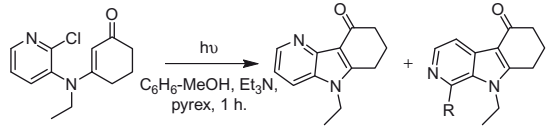
43 (74%)
46 (75%)

44, all-*cis*, (16%)
47, Me *cis* to OH, (20%)
49, Me *cis* to OH, (65%)

Scheme 10

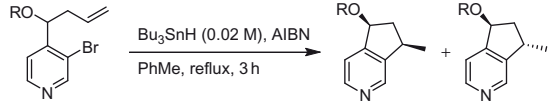
an extensive study on the reactivity of this 2-pyridyl radical in addition reactions to alkenes, an example of which is outlined in Scheme 10.

Reactions were carried out using low concentrations of Bu_3SnH and high dilution conditions. In all cases, *endo*-cyclisation products **43** and **46** were the preferred products. However, when cyclisation precursor **48** was used, the *exo*-product **49** was dominant. In a similar manner, Blache (97JOC8553) submitted 2-chloropyridine derivative **50** to photochemical irradiation in a range of solvents. The amount of cyclised product **51** and its regioisomer **52**, varied with the conditions employed (97JOC8553) (Scheme 11).



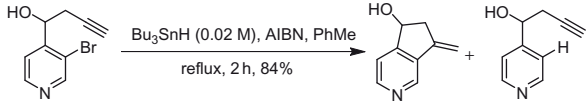
50 **51** (30%) **52,** R=H (19%)
53, R=OMe (13%)
54, R=Ph (6%)

Scheme 11



R=H **55a** overall yield 86% **56a** **57a** **56a:57a** = 3:1
R=*t*-BuMe$_2$Si **55b** quantitative **56b** **57b** **56a:57a** = 3:1

Scheme 12



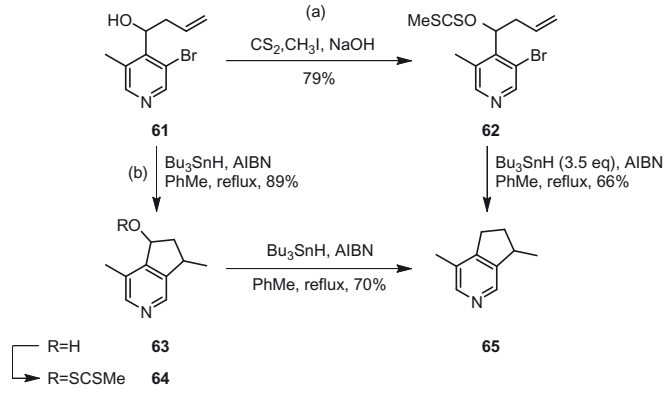
58 **59** **60** **59:60** = 10:1

Scheme 13

Products **51** and **54** can be explained by a radical mechanism involving homolysis of the C–Cl bond. However, the other products cannot be so easily explained and the involvement of a radical cation or anion has been suggested (97JOC8553). Although the presence of a 2-pyridyl σ-radical was not demonstrated conclusively, it cannot be ruled out, leaving this reaction as a rare example of 5-*endo*-trig cyclisation. Some interesting applications of 3-pyridyl radicals are known. Jones (96TL8049) performed an intramolecular addition onto unsaturated bonds from **55a,b** (Scheme 12).

Only 5-*exo*-cyclisation products **56a,b** and **57a,b** are observed. The presence of the bulky protecting group on the alcohol (TBDMS) slightly increases the *cis–trans* isomer ratio, as predicted by the Beckwith model (81T3073). In the same paper, the synthesis of (±)-oxerine has been reported, using an intramolecular radical addition of the 3-pyridyl radical to a terminal alkyne as the key step to give **59** as well as small amounts of the reduced product **60** (Scheme 13).

However, radical addition to alkynes presents two problems compared to alkenes. Firstly, comparable cyclisations are one order of



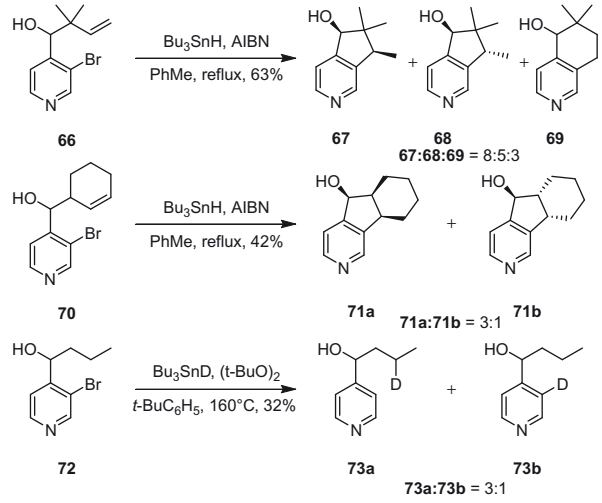
Scheme 14

magnitude slower and secondly, hydrostannylation is competitive. In this case neither 6-*endo* cyclisation, nor hydrostannylation were observed. The only competitive reaction was the direct reduction of **58** to **60** that presumably could be eliminated or minimised by slow addition of Bu_3SnH. Subsequently, the same group completed the synthesis of (±)-actinidine (98T2275), a monoterpene alkaloid isolated from *Actinidia polygama*. The key step was again based on radical addition of a 3-pyridyl radical to an unsaturated bond (Scheme 14).

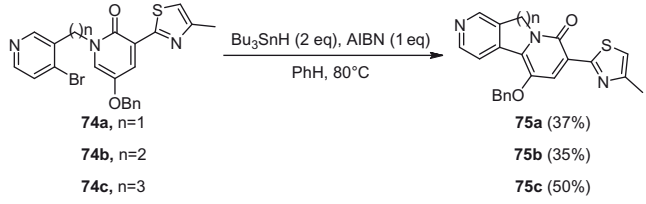
Path **(a)** shows a contemporaneous 5-*exo*-trig radical cyclisation by the 3-pyridyl radical and reduction of the xanthate group by Bu_3SnH, used in large excess (3.5 equiv.) to give **65**. In path **(b)**, **63** was synthesised as an 8:5 mixture of diastereoisomers, that were used in the subsequent step. This route, however, offers a suitable ways to synthesise actinidine as a single enantiomer, starting from **61** as a single enantiomer. The same author (00T397) also carried out a study on the reactivity of this radical (Scheme 15).

The possibility of 1,5-*H*-atom abstraction using this approach was clearly demonstrated *via* reaction of the 3-pyridyl radical precursor **72**, using Bu_3SnD as a radical carrier to form **73a,b**. The result, albeit in low overall yield, suggests that a radical-stabilising group is required on the pyridine ring for cyclisation in this instance. Nadin (99TL4073) used the addition of a 3- or 4-pyridyl radical to a pyridone ring for the synthesis of tricyclic pyridines **75a–c**, a class of molecules used for the construction of the BCD ring portion of the antitumour agent (+)-camptothecin or for the preparation of benzodiazepine receptor ligands (Scheme 16).

It is important to underline that one equivalent of AIBN has been used to aid the oxidation step (rearomatisation). No improvement in yield was achieved by slow addition of Bu_3SnH and an average of 10% of



Scheme 15



Scheme 16

reduced product was typically observed. Interestingly, the highest yield arose from the normally difficult 7-*exo*-trig cyclisation.

An interesting synthesis of pyrazolopyridines has been presented by Alvarez-Builla (02S1093), using an intramolecular radical addition by the 3-pyridyl radical derived from **76a–d** (Scheme 14) as well as 2-pyrazinyl radicals to a pyridine ring, with subsequent rearomatisation to produce cyclised products **77a–c** (Scheme 17).

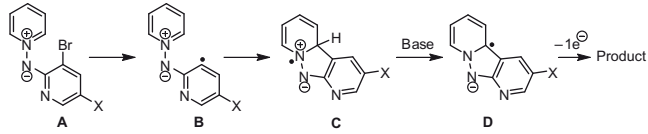
Highest yields were observed when two equivalents of TTMSS, AIBN and K_2CO_3 in acetonitrile–benzene (7:3) were used. An acetonitrile–THF (7:3) mixture gave poor yields of cyclised products, presumably due to *H*-abstraction by the radical from the solvent (THF), while just one equivalent of initiator and radical carrier gave incomplete reaction. In a subsequent paper by the same group (04T11843), the reactivity of the 3-pyridyl radical in a different environment was explored (Scheme 18).

These results represent the first examples of pyridyl radical *ipso*-substitution on a sulphonamide, a known process performed by aryl

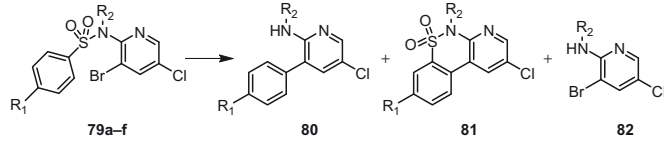
Entry	Starting Material	Conditions	77	78
1	**76a**, X=Cl	a	**77a** (56%)	**78a** (5%)
2	**76a**, X=Cl	b	**77a** (18%)	**78a** (2%)
3	**76a**, X=Cl	c	**77a** (2%)	**78a** (60%)
4	**76b**, X=H	a	**77b** (21%)	**78b** (21%)
5	**76c**, X=Ph	a	**77c** (23%)	-
6	**76d**, X=Br	d	**77b** (20%)	-

Conditions: (a)TTMSS (2 eq), AIBN (2 eq), K_2CO_3 (2 eq), CH_3CN:PhH (7:3); (b) TTMSS (1 eq), AIBN (1 eq), K_2CO_3 (2 eq), CH_3CN:PhH (7:3); (c) TTMSS (2 eq), AIBN (2 eq), CH_3CN:PhH (7:3); (d) TTMSS (2 eq), AIBN (2 eq), K_2CO_3 (2 eq), CH_3CN:THF (7:3)

Proposed mechanism:



Scheme 17

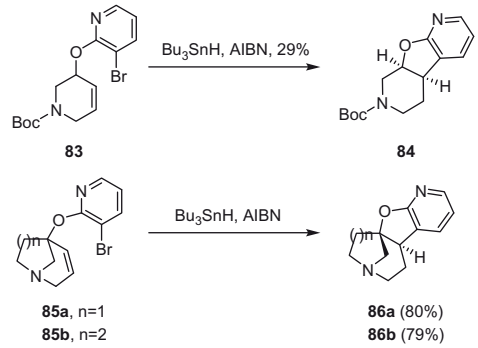


Entry	Starting material	80	81	82
1	**79a**, R_1=R_2=H	-	**a** (33%)	**a** (7%)
2	**79b**, R_1=R_2=CH_3	**b** (67%)	**b** (20%)	-
3	**79c**, R_1=CH_3, R_2=CH_3	**c** (63%)	**c** (18%)	-
4	**79d**, R_1=OCH_3, R_2=CH_3	**d** (60%)	**d** (13%)	-
5	**79e**, R_1=Cl, R_2=CH_3	**e** (50%)	**e** (20%)	-
6	**79f**, R_1=NO_2, R_2=CH_3	**f** (33%)	-	-

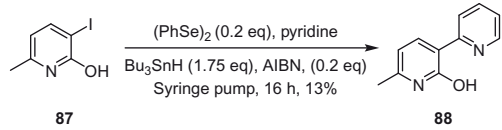
Conditions: TTMSS (8 eq), AIBN (4 eq), *m*-xylene, 29 h by syringe pump, 24 h, 80 °C

Scheme 18

radicals (91CC877, 97TL141). The large amounts of initiator required could be explained by its possible participation in the rearomatisation (oxidation) mechanism. Moreover, with sulphonamide **79a** the desired reaction does not happen, and only a small amount of the 6-*exo* addition product to the aromatic ring is found.



Scheme 19



Scheme 20

Cases (03TL2995) used a 3-pyridyl radical to perform a 6-*exo*-trig addition onto an endocyclic C═C bond to produce cyclised products **84** and **86a,b** (Scheme 19).

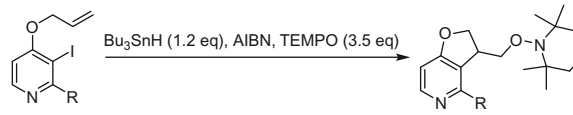
Cyclised products **84** and **86a,b** were unusually obtained as single diastereoisomers, which can be explained by the strain present in the transition state, which strongly prefers a specific conformation (03TL2995).

Crich studied the intermolecular reaction of the radical derived from pyridine **87** with pyridine, using diphenylselenide in substoichiometric amounts in the presence of Bu_3SnH and AIBN (04H(64)499). Diphenyldiselenide increased the yields of addition product **88**, compared to experiments in its absence, implicating its participation in the re-aromatisation step (Scheme 20).

Surprisingly, only regioisomer **88** was obtained, albeit in low yield. Higher yields were observed when a 2-thienyl radical was employed.

Dodd (04H(64)261) carried out a 5-*exo* radical cyclisation of the 3-pyridyl radical from **89a,b** in his synthesis of a conformationally constrained analogue of homoquinolinic acid **90a,b**, a selective NMDA subtype receptor agonist (Scheme 21).

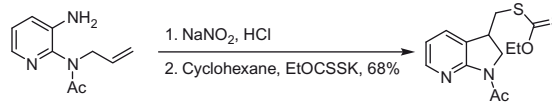
Addition of TEMPO to the reaction resulted in concomitant trapping of the cyclised primary radical, which was used to introduce a handle for further synthetic manipulations.



89a, R=CONHPh
89b, R=CO_2Bn

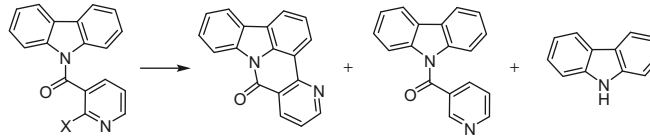
90a (78%)
90b (50%)

Scheme 21



91 **92**

Scheme 22



93, X=Cl
97, X=Br

94 (90)
98 (99)

95 (2)
99 (1)

96 (2)
100 (0)

Conditions: Bu_3SnH, ACCN, PhMe.

Scheme 23

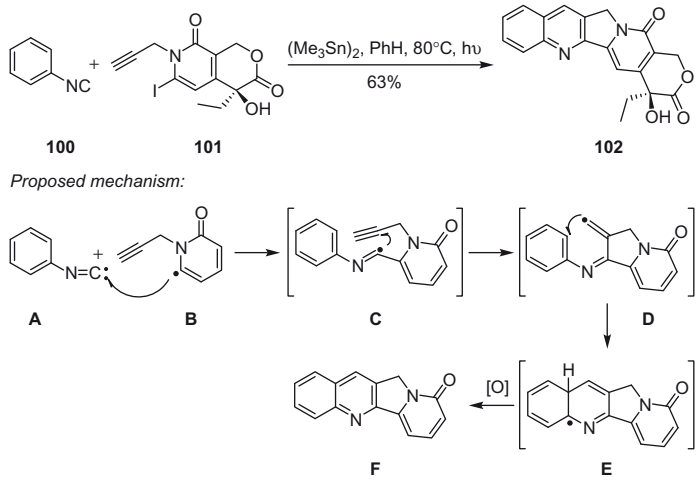
In a modification of the Leuckart reaction (98AGE3072, 88CRV765, 86JA5890, 86JA8227, 02S835), Zard (05TL971) generated a 3-pyridyl radical from amine **91**, which underwent addition to the terminal alkene in **91** to give **92** (Scheme 22).

The original procedure and conditions were cleverly converted into a biphasic system, in order to control the reactivity of the intermediate aromatic radical, to maintain a low concentration. This useful methodology was applied to the synthesis of azaindoline **92**, in good yield.

In an approach to polycyclic systems, Markgraf (05T9102) exploited additions to aromatics by a number of different pyridyl radicals and the following example is illustrative (Scheme 23).

Markgraf used chloropyridine **93** as a radical precursor, which is an unusual feature when highly energetic aromatic radicals are involved. Unsurprisingly the yields of cyclisation product **94** were lower than when cyclisation precursor bromide **97** was used.

As part of the scope of this review, the extensive studies by Curran towards the synthesis of camptothecin and its analogues by radical



Scheme 24

cascade reaction of aryl isonitriles, involving 6-pyridonyl radicals are included (96AGE2683, 96T11385, 98CEJ67, 97T8881, 02BMC103, 05BML4736, 03SL1299). A number of derivatives (96T11385, 98CEJ67, 03SL1299) have been synthesised in the Curran group and their biological activities tested demonstrating the utility of pyridyl radical cyclisations (02BMC103, 05BML4736). Variations around the core structure were explored to demonstrate the high degree of tolerance of this unusual radical cascade reaction. Synthesis of the camptothecin analogue, mappicine, was carried out using analogous methodology (97T8881). In the above scheme (Scheme 24), the synthesis of (*S*)-20-camptothecin (**102**) is highlighted as an example of this powerful methodology (96AGE2683, 96T11385, 98CEJ67).

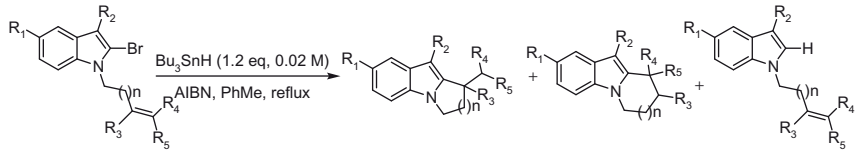
(*S*)-20-Camptothecin **102** was obtained in good yield. The reaction mechanism involves radical addition of the 2-pyridonyl radical **B** to isonitrile **A**, to form radical intermediate **C**. 5-*Exo*-dig cyclisation onto the alkyne produces vinyl radical **D**. Addition onto the aromatic ring with subsequent rearomatisation, affords the final product **F**. It is noteworthy that three new carbon–carbon bonds have been generated in remarkably good yield for such a complex cascade series of events. Mechanistic studies of this reaction have revealed some interesting features. Iodine was the optimum halide precursor for generation of the 6-pyridonyl radical. Cyclisation resulting from bromide derivatives were less successful, while chlorides were unreactive. Benzene proved to be the best solvent, while unexpectedly, *t*-butanol gave lower yields. Use of hexamethylditin as the radical carrier led to higher yields, while hexabutyldistannane and tris(trimethylsilyl)silane gave on average 10% lower yields.

3. INDOLYL RADICALS

Indolyl radicals, as pyridyl radicals, are amongst the most widely explored heteroaromatic radicals. They have frequently been used as intermediates for the synthesis of a number of natural compounds and the Jones group have published extensively in this area as outlined below.

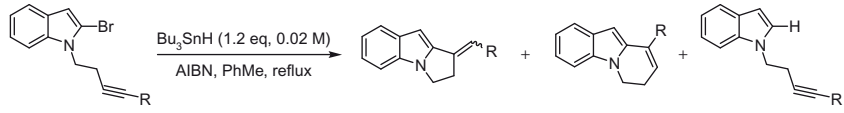
Intramolecular radical addition to isolated unsaturated bonds in the synthesis of pyrroloindoles – a ring system found in the biologically active mitosenes has been studied in detail (95TL4857), (98T2149) (Scheme 25).

Under the conditions employed, mixtures of *exo*-cyclisation products **104a–i**, *endo*-cyclisation products and reduced products **105a–i** from bromoindoles **103a–i** were obtained. Note that substitution on the double



103a-i **104a-i** **not observed** **105a-i**

Entry	Starting Material	Yield	*exo*	*endo*	Reduced
1	**103a**, R_1=R_2=R_3=R_4=R_5=H, n=1	79%	**104a**	-	**-**
2	**103b**, R_1=R_2=R_3=R_4=R_5=H, n=2	74%	**104b** (3.5)	-	**105b** (1)
3	**103c**, R_1=R_2=R_3=R_4=R_5=H, n=3	78%	**-**	-	**105c**
4	**103d**, R_1=R_2=R_3=H,R_4=R_5=CH_3, n=1	71%	**104d**	-	**-**
5	**103e**, R_1=R_2=R_4=R_5=H,R_3=CH_3, n=1	73%	**104e**	-	**-**
6	**103f**, R_1=R_3=R_4=R_5=H,R_2=CH_3, n=1	73%	**104f**	-	**-**
7	**103g**, R_1=R_3=R_4=R_5=H,R_2=CH_3, n=2	64%	**104g** (2.5)	-	**105g** (1)
8	**103h**, R_1=OCH_3,R_2=R_3=R_4=R_5=H, n=1	91%	**104h**	-	**-**
9	**103i**, R_1=OCH_3,R_2=R_3=R_4=R_5=H, n=2	96%	**104i** (3)	-	**105i** (1)



Entry 10 **106a,** R=H, yield=0% **107a -** **108a -** **108c -**

Entry 11 **106b,** R=TMS, yield=trace **107b** (trace) **108b -** **108d -**

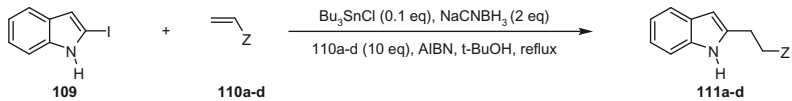
Scheme 25

bond led to 5-*exo*-cyclised products in all cases. However, in contrast, in the case of 5-substituted 5-hexenyl radicals, a mixture of 5-*exo*- and 6-*endo*-cyclisation products was observed (85T3925). This has been ascribed to the bond angles involved in the 5-membered ring in this particular system, which incorporates a rigid indole ring. In the case of entry 2, the product of 6-*exo* cyclisation **104b** was found together with reduction product **105b**, indicating the lower rate of this reaction, while none of the 7-*endo* product was observed. Further extension of the alkyl chain gave only reduced products, highlighting a further reduction in the rate constant for larger cyclisations. Alkynes were also investigated as radical acceptors. Protection with TMS was necessary to prevent hydrostannylation. However, the expected 5-*exo* product was only found in trace amounts, presumably due to decomposition of vinylsilane during the reaction. It is also of interest to note that substitution on the indole ring (entries 6–9) gave no appreciable difference in the yields and product distributions.

The role of the halogen atom in the precursors was also explored. Although bromine was mostly used, iodine and chlorine were also employed. While the former gave very efficient cyclisation (but with a far more complex mixture of products), the latter gave no reaction at all, reflecting the order of C–X bond strength, Cl > Br > I.

From the same group, the first example of intermolecular radical additions of indolyl radicals to double bonds has been reported (99CC1761) (Scheme 26).

Reaction of indole **109** with a number of alkenes **110a–d** is described (99CC1761). The expedient use of a catalytic amount of Bu_3SnCl in the presence of reducing agent $NaCNBH_3$, ensured that the lowest concentration of Bu_3SnH was obtained (86JA303). Further examples are available in the original report, outlining the reactivity of the 2-indolyl radical towards a number of alkenes. Noteworthy in their approach, is



109 **110a-d** **111a-d**

Entry	Starting Material	Radical acc.	Product	Yield
1	**109**	**110a**, Z=CN	**111a**, Z=CN	30%
2	**109**	**110b**, Z=CO_2Et	**111b**, Z=CO_2Et	25%
3	**109**	**110c**, Z=CO_2*t*-Bu	**111c**, Z=CO_2*t*-Bu	18%
4	**109**	**110d**, Z=SO_2Ph	**111d**, Z=SO_2Ph	25%

Scheme 26

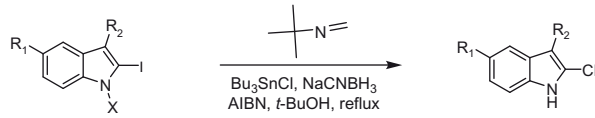
the synthesis of 2-cyanoindoles **113a–c** using this methodology (Scheme 27).

Unsubstituted and 5-methoxy indoles gave acceptable yields of cyanoindoles **113a** and **113b**, while the 3-methylindole derivative **112d** proved to be a poor substrate. Surprisingly, in the case of *N*-phenylsulphonyl indole precursor **112c** none of the expected product was observed, but small amounts of unsubstitutued 2-cyanoindole **113a** were obtained as well as the reduction product. The authors propose a possible radical cleavage of the N–S bond as outlined in Figure 1.

Following their investigation on the reactivity of 2-indolyl radicals, Jones (00TL4209) reported on their intramolecular addition reactions to benzene rings tethered to the nitrogen of the indole with various length chains (Scheme 28).

Reaction of **114a** in cyclohexane, resulted in reduced **115a**, due to *H*-atom abstraction from solvent. Use of acetonitrile proved crucial to the outcome of cyclisation. Note that for n=3 (**114c**), the expected 1,5-*H* atom abstraction from the benzylic position did not take place and 37% of 7-membered product **116c** along with 32% of reduced product **115c** was obtained. In addition, for n=4 (**114d**), the major product **117d** arose from 1,5-*H* atom abstraction followed by subsequent cyclisation onto the indole ring, followed by rearomatisation.

An additional example of 1,5-*H* atom abstraction by a 2-indolyl radical has been described by Gribble (01CC805) (Scheme 29).



112a–d **113a–c**

Entry	Starting Material	Product	Yield
1	**112a**, R_1=R_2=H, X=H	**113a**, R_1=R_2=H, X=H	38%
2	**112b**, R_1=OMe, R_2=H, X=H	**113b**, R_1=OMe, R_2=H, X=H	40%
3	**112d**, R_1=H, R_2=Me, X=H	**113c**, R_1=H, R_2=Me, X=H	10%
4	**112c**, R_1=R_2=H, X=SO_2Ph	*N*-phenylsulfonylindole **113a**	90% trace

Scheme 27

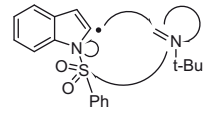
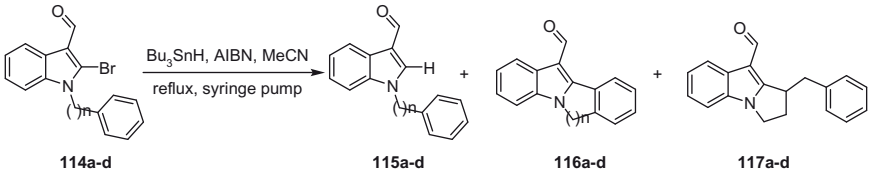
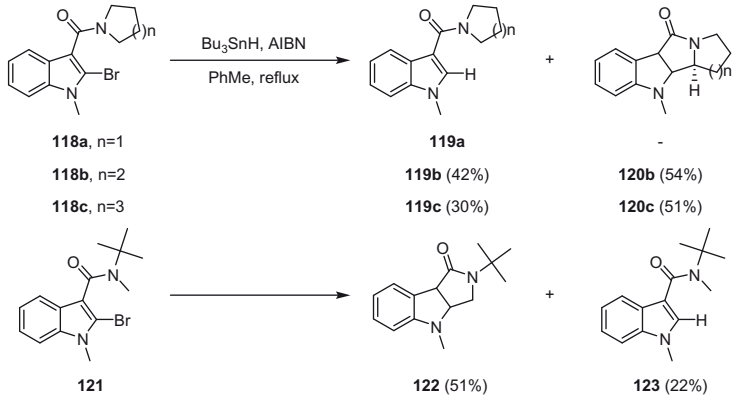


Figure 1



Entry	Starting Material	Reduction	Radical addition	1,5-*H* Atom abstraction
1	**114a**, n=1	**115a**(55%)	**116a**(25%)	-
2	**114b**, n=2	**115b**(20%)	**116b**(65%)	-
3	**114c**, n=3	**115c**(32%)	**116c**(37%)	-
4	**114d**, n=4	**115d**(27%)	-	**117d**(48%)

Scheme 28



Scheme 29

In contrast to Jones' reports, the alkyl radical generated from the 1,5-*H* atom abstraction undergoes addition to the indole ring, without rearomatisation. However, some doubts about the mechanism are described. Direct *5-endo*-trig or *4-exo*-trig leading to a spiro *β*-lactam intermediate, followed by 1,2-alkyl migration (ring expansion) are possible mechanisms.

The indole-containing alkaloid rutaecarpine **126** has been synthesised *via* cyclisation of a 2-indolyl radical onto the 2-position of a 4-quinazolinone (07OBC103). The radical precursor **124** was prepared by *N*-alkylation of the 3-position of the 4-quinazolinone followed by bromination of the 2-position of the indole ring. Slow addition of Bu_3SnH gave 15% of rutaecarpine **126** and 57% of the reduced product **125**.

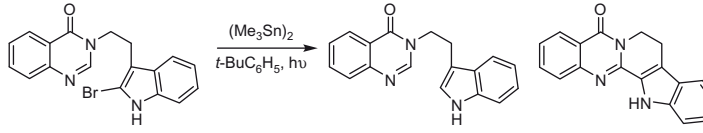
However, reaction with $(Me_3Sn)_2$ at reflux in *t*-butylbenzene and with sunlamp irradiation gave rutaecarpine **126** in 57% yield with none of the reduced product (Scheme 30).

In one of the earliest reports on indole radicals, Sundberg (90JOC6028) outlined an intramolecular radical addition of a 3-indolyl radical onto an isolated double bond (for the synthesis of analogues of *Iboga* alkaloids) to yield **128a–c** providing a rare example of an 8-*endo*-trig cyclisation (Scheme 31).

Srinivasan (96TL2659) synthesised a series of 4-substituted *β*-carboline derivatives using the radical addition of 3-indolyl radicals to an isolated double bond, in a 6-*exo*-trig fashion to give tricyclic **130a–c** and **132** (Scheme 32).

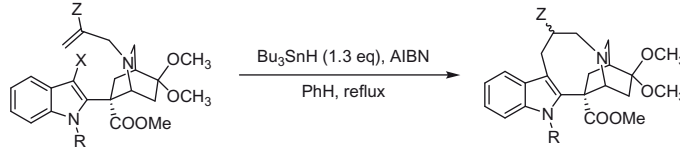
Use of SPh instead of Br in the 3-position of the indole **129b** was attempted, but no reaction occurred, underlining the fact that only weak bonds can be cleaved under these conditions to generate heteroaromatic radicals. In a subsequent paper produced by the same group (04SC1325), a radical addition to aromatic rings was reported, to give *β*-carboline derivatives **134a–c** and **135a–c** (Scheme 33).

Note that large amounts of desulphonylated *β*-carbolines **135a–c** were obtained, which is precedented (00T979). In the synthesis of



124 **125** **126**

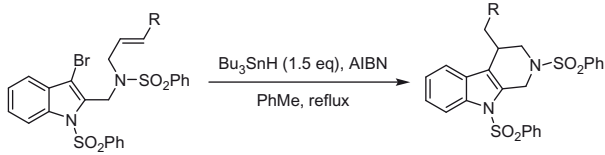
Scheme 30



127a–e **128a–c**

Entry	Starting Material	Product
1	**127a**, R=H, X=I, Z=CO_2Et	**128a**(48%), 2 isomers
2	**127b**, R=CH_3, X=I, Z=CO_2Et	**128b**(42%), 2 isomers
3	**127c**, R=H, X=I, Z=SO_2Ph	**128c**(70%), 20:1 isomeric ratio
4	**127d**, R=CH_3, X=I, Z=H	-
5	**127e**, R=H, X=I, *N*-propargyl	-

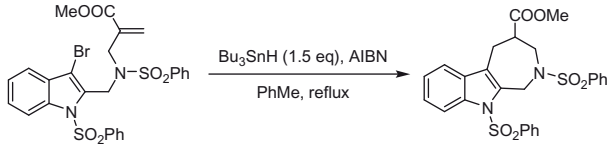
Scheme 31



129a, R=CH_3 **130a** (40%)

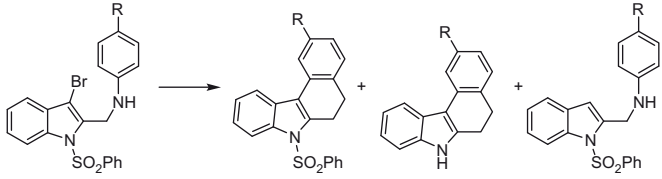
129b, R=CH_2CO_2Me **130b** (70%)

129c, R=CH_2Ph **130c** (60%)



131 **132** (60%)

Scheme 32



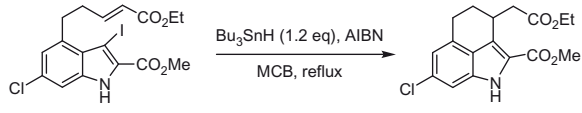
133a, R=H **134a** (25%) **135a** (33%) **136a** (12%)

133b, R=CH_3 **134b** (15%) **135b** (40%) 136b (15%)

133c, R=$CH(CH_3)_2$ **134c** (14%) **135c** (47%) **136c** (16%)

Conditions: Bu_3SnH (2 eq), AIBN, PhMe, reflux, 48h.

Scheme 33



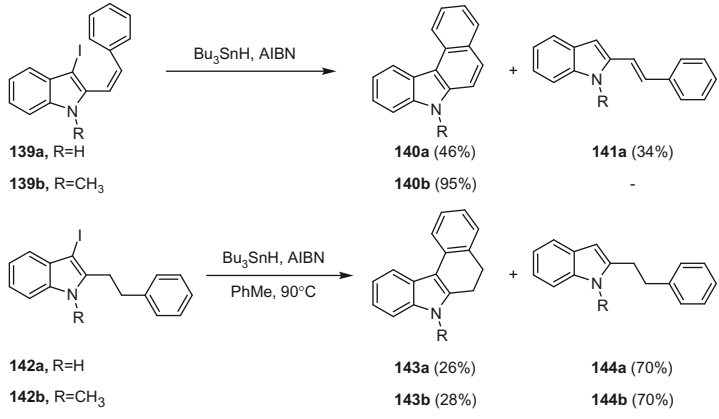
137 **138** (80%)

Scheme 34

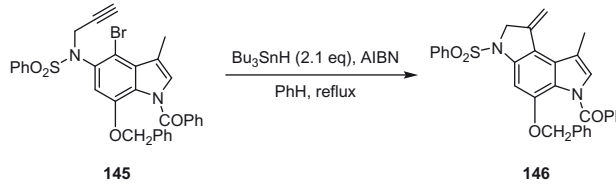
indole-2-carboxylic acids as potent NMDA-glycine antagonists, Nagata (01JOC3474) reported an intramolecular radical addition of a 3-indolyl radical from **137** onto a double bond to produce **138** (Scheme 34). The reaction was fast (1 h) and 6-*exo*-trig cyclisation product **138** was

recovered as well as the product of reduction (7:3 ratio at 100°C, 0.2 M). Another application of 3-indolyl radicals is described by Harrowven (03TL1795), *via* intramolecular addition to a benzene ring (Scheme 35). Noteworthy is the observation that cyclisation of **139a** resulted in the formation of *trans*-styrylindole **141a**, while reaction of **139b** led to cyclised product **140b** as the exclusive product. Isomerisation of the alkene double bond by addition–elimination of the tributylstannyl radical is competitive with C–I bond homolysis when the double bond is in a planar conjugation to the indole ring. In contrast, substitution at the indole nitrogen makes this conformation less favourable and slows the rate constant for the formation of the by-product. The *cis*-conformation of the alkene **139a**,**b** is essential for success. When the reaction was repeated with an alkyl chain in the 2-position (precursors **142a,b**), cyclised products **143a,b** were recovered in poor yields, confirming the observation that a higher degree of freedom of the alkyl chain is a disadvantage in this reaction.

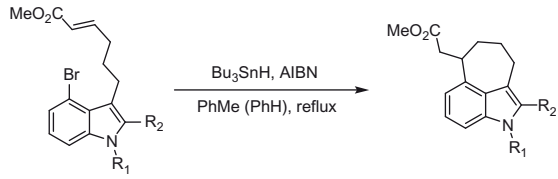
In early studies on the 4-indolyl radical, Boger (88JA1321) synthesised the antitumour-antibiotic CC-1065, using an intramolecular radical addition to an alkyne in a 5-*exo*-dig cyclisation (Scheme 36).



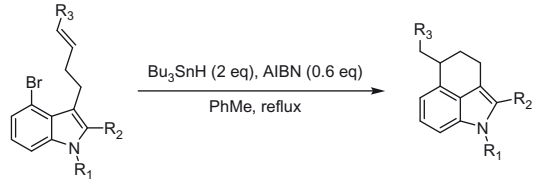
Scheme 35



Scheme 36

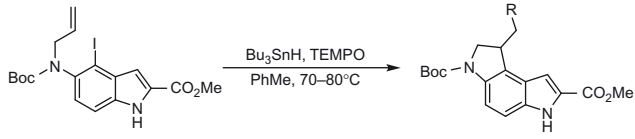


147a, R_1=Ts, R_2=H -
147b, R_1=H, R_2=CO_2Et -



148a, R_1=Ts, R_2=H, R_3=CHO **149a** (51%)
148b, R_1=H, R_2=CO_2Et, R_3=CHO **149b** (71%)
148c, R_1=Ts, R_2=H, R_3=CO_2Me **149c** (63%)

Scheme 37



150 **151** (R=TEMPO)

Scheme 38

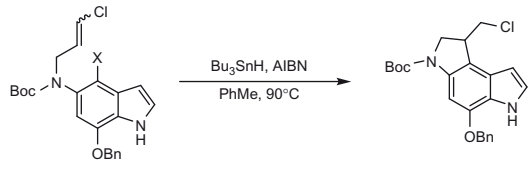
The absence of protecting groups on terminal alkyne **145** is noteworthy. However, the yield was not reported, due to the instability of **146** under chromatography, and it was used without further purification (overall yield 40%).

Yokoyama (97H(46)133) reported the synthesis of the skeleton of lysergic acid, using an intramolecular 6-*exo*-trig radical addition of a 4-indolyl radical onto a double bond (Scheme 37).

Reaction of **147a,b** was ineffective, while substrates **148a–c** gave **149a–c**. This behaviour is unsurprising, due to the observation that 7-*exo* cyclisations are slow and more difficult compared to 6-*exo* cyclisations.

Tercel (99JOC5946) carried out a synthesis of the amino analogue **151** of the antitumour antibiotic duocarmycin SA, amino-*seco*-DSA (Scheme 38).

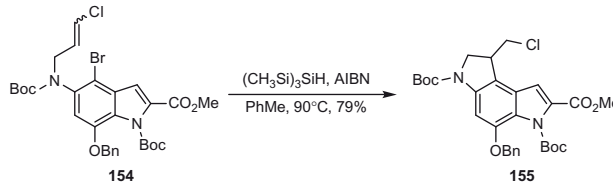
Four equivalents of Bu_3SnH were initially used (addition over 3 h) as well as five equivalents of TEMPO, but the presence of remaining starting material led the authors to add further portions of TEMPO (1.5 equiv.) and Bu_3SnH (1.1 equiv., dropwise during 2 h), to finally obtain



152a, X=I
152b, X=Br

153a (72%)
153b (77%)

Scheme 39



154 **155**

Scheme 40

151 in an excellent 77% yield. The final radical is trapped by TEMPO and can therefore undergo additional synthetic manipualtions.

In a similar manner, Boger synthesised a subunit of CC-1065 and duocarmycins (99JOC2227, 00JOC4101). The key step is, again, intramolecular radical cyclisation of the 4-indolyl radical to a double bond from **152a,b**, in a 5-*exo*-trig cyclisation to give **153a,b** (Scheme 39).

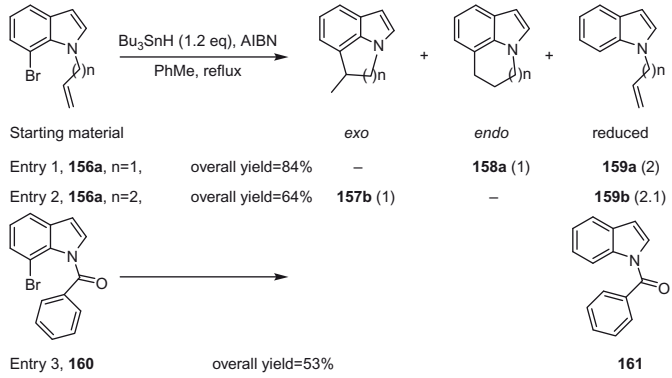
Use of catalytic conditions described by Fu and co-workers (97JA6949) for substrate **152a** (0.1 equiv. of $(Bu_3Sn)_2O$ and poly (methylhydroxysiloxane) (PMHS)) resulted in a reduction in the yield (55%).

In a similar strategy, Tietze (03EJO562) used TTMSS in his synthesis of *seco*-duocarmycin SA (Scheme 40).

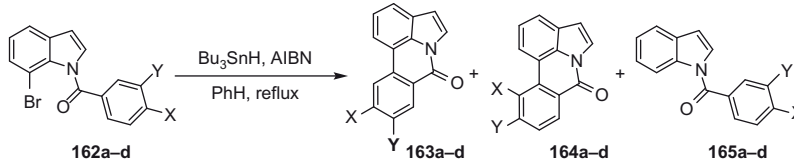
Use of TTMSS gave comparable yields of **155** to the Bu_3SnH procedure, avoiding the complications associated with organotin hydrides.

There are scant reports in the literature on 7-indolyl radicals. Jones (97TL5379) reported the first radical addition of this type onto unsaturated bonds (Scheme 41).

As shown in entry 1, the kinetically favoured 5-*exo*-trig cyclisation does not occur. Instead, a 1:2 ratio of 6-*endo*-cyclisation product **158a** and reduced product **159a** was observed. The authors attribute this to high ring strain in final 5-*exo* product (and the transition state leading to its formation). Comparison between these results and those obtained by Black (92T7601) and Dankwardt (95JOC2312), where 6-membered rings were obtained using palladium-catalysed cyclisations on similar substrates, indicate that ring constraint is responsible for the product distribution. Synthesis of pratosine, an alkaloid from the pyrrolophenanthridone family, was attempted (entry 3).



Scheme 41



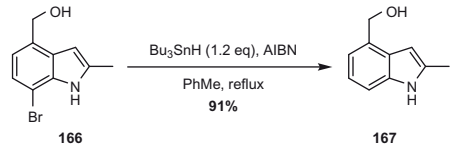
Entry	Starting Material	163a–d	164a–d	165a–d
1	**162a**, X=Y=H	**a** (48%)	–	**a** (21%)
2	**162b**, X=OMe, Y=H	**b** (52%)	–	**b** (8%)
3	**162c**, X=Y=OMe	**c** (42%)	**c** (26%)	**c** (2%)
4	**162d**, XY=OCH2O	**d** (29%)	**d** (20%)	**d** (20%)

Scheme 42

As shown, only reduced product **161** was recovered. In contrast, Tsuge (98CL155) carried out the same reaction to produce the pyrrolophenanthridone skeleton nucleus of a series of active alkaloids (hippadine, pratosinine, pratorimine and pratorinine) (Scheme 42).

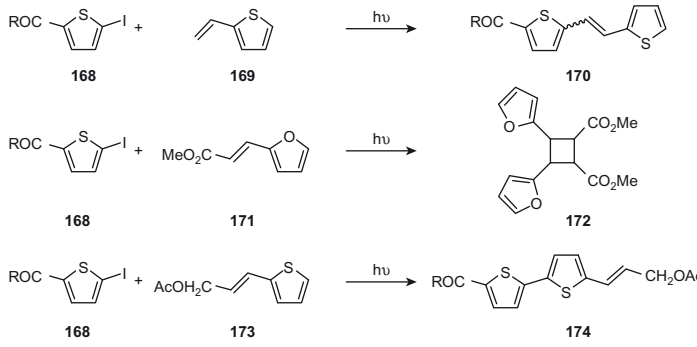
The reason for these apparently contradictory results is the different conditions used to perform the radical cyclisation. In Jones' studies, 1.2 equiv. of Bu_3SnH and trace amounts of AIBN were used, while in Tsuge's work, 1.5 equiv. of Bu_3SnH and 0.25 equiv. of initiator were used. This difference could explain the disparity, since the initiator probably takes part in the oxidation mechanism.

Dobbs has reported a short synthesis of several complex indoles (01JOC638). The radical reduction follows the Bartoli synthesis (89TL2129, 91JCS(P1)2757) of several indole derivatives and the following example is illustrative (Scheme 43).



166 167

Scheme 43



168 169 170 168 171 172 168 173 174

Scheme 44

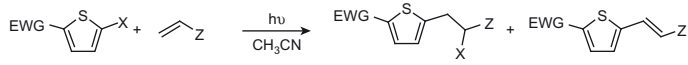
The utility of this method is noteworthy, as a number of functional groups are tolerated during the radical reaction and it proceeds under very mild conditions and in high yields.

4. THIENYL RADICALS

Thienyl radicals are less common in organic synthesis compared to those in the previous two sections. An early example involves the photochemical generation of a 2-thienyl radical from 2-iodothiophene and subsequent addition to solvent (benzene) in a radical addition–rearomatisation reaction (65JOC2493). In an extensive study D'Auria (00EJO1653) examined the photochemical behaviour of 2-halothiophene derivatives **168** in the presence of alkenes or aromatic compounds as outlined in Scheme 44.

In initial experiments, derivative **168** was irradiated in the presence of alkenes with a range of electron densities. Optimum results were obtained with electron-rich alkene **169**, while no reaction was observed in the case of electron-poor alkene **171**, where **172** was the only product. In the reaction with **173**, dimerisation to produce **174** was observed. This behaviour indicated that the 2-thienyl radical is electrophilic (Scheme 45).

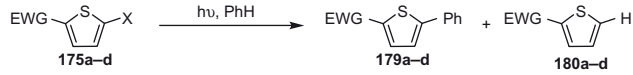
The 2-thienyl radical can also react with electron-poor double bonds. Distribution of products **177** and **178** depends on the nature of the two



175 **176** **177** **178**

Z=CO_2Me, COMe, CHO; EWG=COMe, CHO, NO_2

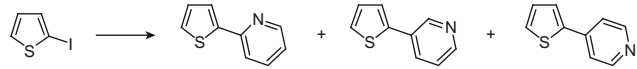
Scheme 45



175a–d **179a–d** **180a–d**

Entry	Starting Material	179	180
1	**175a**, X=I, EWG=CHO	**a**	–
2	**175b**, X=Br, EWG=CHO	**b**	–
3	**175c**, X=Cl, EWG=CHO	–	**c**
4	**175d**, X=I, EWG=CN	–	**d**

Scheme 46



181 **182** (19%) **183** (24%) **184** (7%)

Conditions: Bu_3SnH (1.75 eq), AIBN, (0.2 eq), $(PhSe)_2$(0.2 eq), pyridine, syringe pump, 16h.

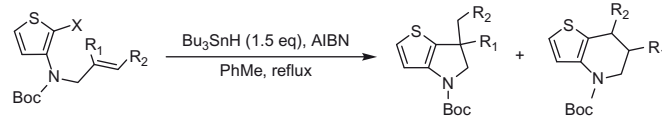
Scheme 47

reagents and solvent. Irradiation in benzene (97H(45)1775) affords products of addition, but, in some cases, dehalogenation to give **180a–d** is also observed (Scheme 46).

While **175a** and **175b** gave addition to solvent, **175c** and **175d** gave dehalogenation products *via H*-abstraction from the solvent. In an analogous manner to reaction of pyridyl radicals, Crich (04H(64)499) carried out a thienyl radical addition to pyridine to produce regioisomers **182**, **183** and **184** (Scheme 47). Unfortunately, poor regioselectivity was observed, in contrast to the reaction with the 3-pyridyl radical.

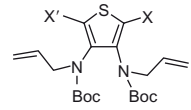
Paulmier (01JCS(P1)37) described the synthesis of the thieno(3,2-*b*) pyrrole skeleton **186a–f** from thiophene radical precursors **185a–f**, using Bu_3SnH (Scheme 48).

It is interesting to note that, in the cases when R_1=R_2=H, with either a Br, I or SePh radical precursor, comparable yields of cyclised products **186a–f** (68, 73 and 69%, respectively) were obtained. However, when R_1=Me, 6-*endo*-trig cyclisation occurred to give the piperidine derivative **187b**, while the 5-*endo*-trig **186b** was observed in trace amounts (5%). Radical addition–cyclisation to the double bond of dicarbamates **188a–c** was unsuccessful.



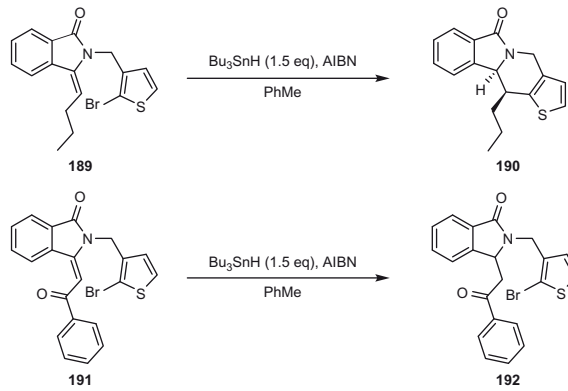
185a–f **186a–f** **187a–f**

Entry	Starting Material	5-*exo*	6-*endo*
1	**185a**, R_1=R_2=H, X=Br	**186a** (68%)	–
2	**185b**, R_1=R_2=H, X=I	**186a** (73%)	–
3	**185c**, R_1=R_2=H, X=SePh	**186a** (69%)	–
4	**185d**, R_1=CH_3, R_2=H, X=Br	**186b** (5%)	**187b** (76%)
5	**185e**, R_1=H, R_2=CH_3, X=Br	**186c** (67%)	–
6	**185f**, R_1=H, R_2=Ph, X=Br	**186d** (85%)	–



188a, X=I,X′=H
188b, X=X′=Br
188c, X=X′=I

Scheme 48

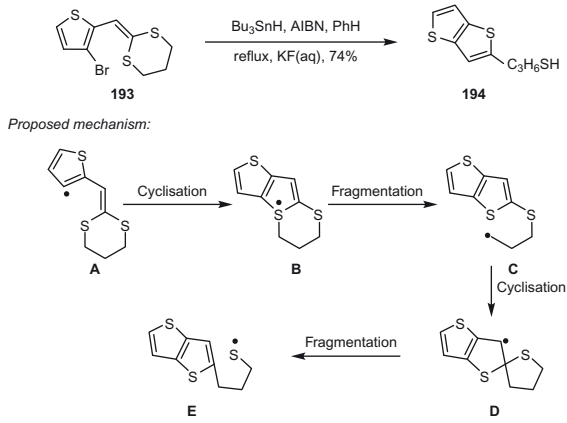


189 **190** **191** **192**

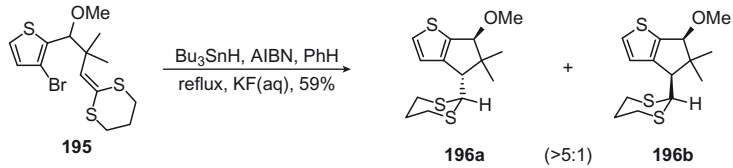
Scheme 49

An interesting use of a 2-thienyl radical is provided by Decroix (96TL7707) in the synthesis of indolizidine **190** (Scheme 49).

The product of the 6-*endo*-trig cylisation was isolated as a single diastereomer from a complex mixture. Unfortunately no yields are reported. Of note, use of the same procedure for enamidone **191** afforded only reduction of the double bond, without evidence of cyclised product or dehalogenation. However, a similar reduction of a carbon–carbon double bond has been reported (87TL1313). The same reaction carried out in benzene, gave reduction of the radical precursor.



Scheme 50



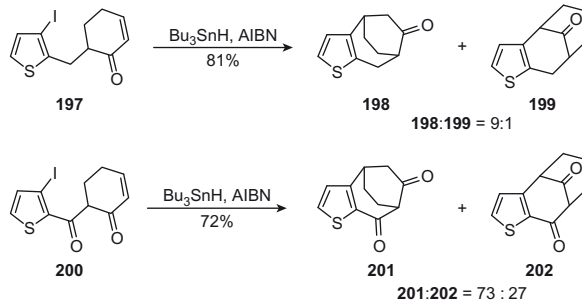
Scheme 51

Harrowven (93TL5653) has reported an interesting 'cascade' radical reaction involving ketenethioacetals. The mechanism is similar to that described for pyridyl radicals (Scheme 3). The cascade reaction starts from the intramolecular addition of the 3-thienyl radical to a sulphur atom (88CL1637, 85CC1390, 85TL1761, 84JA4218, 66JA4096, 70TL3677) and subsequent fragmentation to produce a carbon-centred radical, which undergoes cyclisation (Scheme 50).

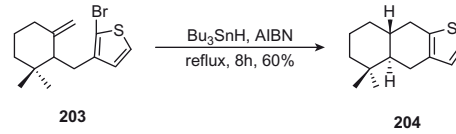
2-Thienyl and 2-pyridyl (Scheme 3) radicals were used to explore the utility of this reaction. Note that for both, 5-*exo*-trig cyclisation is preferred. The reason was presumed to be electronic in nature. Interestingly, the only product from the 2-thienyl radical was **194**.

The same group has also published another study on ketenethioacetals (94TL5301). Choosing the appropriate substrate, it was possible to avoid the sequential radical addition–fragmentation at the sulphur atom, as already described (Scheme 3). A diastereomeric mixture of predicted 5-*exo*-trig products **196a,b** were obtained in good yield (Scheme 51).

Duffault (98SC2467) reported a 3-thienyl radical addition onto cyclohexenones *via* the 3-thienyl radical (Scheme 52). The products of 7-*endo*-trig addition **198** and **201** were clearly predominant.



Scheme 52



Scheme 53

Ray (05SL1951) used a thienyl radical to complete the synthesis of the thiophene analogue of glaucescenolide **204**, a bioactive natural product, obtained as the sole isolable compound (Scheme 53).

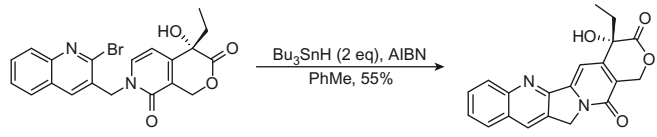
5. QUINOLYL AND ISOQUINOLYL RADICALS

Initial reports on quinolyl and isoquinolyl radicals were first published in the 1970s (75JA1548, 73JA6863, 72JOC3199), but their use in the synthesis of heterocycles was first reported by Comins (94TL5331), where the synthesis of (*S*)-camptothecin **206** is described. The radical step takes place in the construction of the *C* ring (Scheme 54).

Following 5-*exo*-trig cyclisation, the radical undergoes oxidation. Typically, at least one equivalent of initiator is required. However, participation of Bu_3SnH is not excluded.

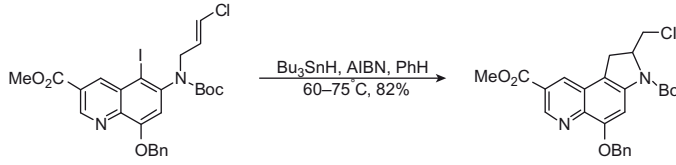
Boger (98TL2227) used a 5-quinolyl and a 4-indolyl (Scheme 39) radical in a 5-*exo*-trig cyclisation to obtain **208**, the tricycle moiety that is part of the more complex structure of CC-1065 and duocarmycin analogous, which are potent antitumour antibiotics (Scheme 55).

Bennasar (00CC2459, 02JOC7465) reported a 5-*exo*-trig cyclisation of a 2-quinolyl radical onto a 2-pyridone with contemporaneous desulphurisation of substrate **209a–c**, to synthesise the camptothecin precursor **210a–c**, further manipulated to afford (±)-20-deoxycamptothecin (Scheme 56).



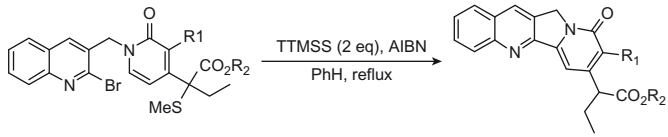
205 **206**

Scheme 54



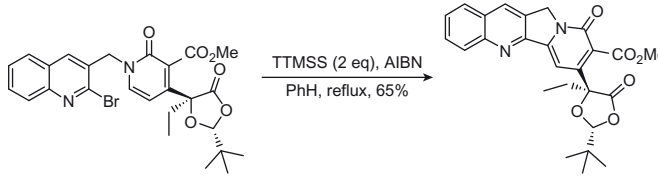
207 **208**

Scheme 55



209a, R_1 = CO_2Me, R_2 = CH_3
209b, R_1 = CO_2Me, R_2 = i-Pr
209c, R_1 = R_2 = CH_3

210a (70%)
210b (65%)
210c (65%)



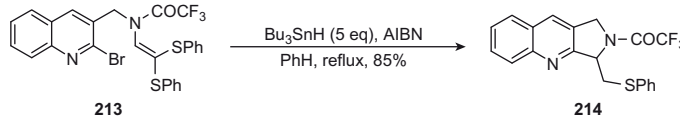
211 **212**

Scheme 56

In this case TTMSS was used instead of Bu_3SnH, to provide increased yields. Radical cyclisation of **211** to give **212** is the key step in the total synthesis of (+)-camptothecin (02JOC7465).

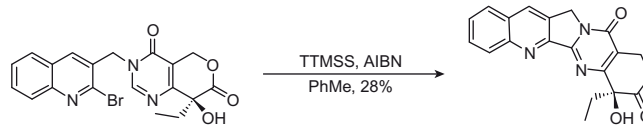
Ishibashi (03JOC7983) highlights an example of a 2-quinoline radical addition to an alkene bearing two phenylthio groups (Scheme 57).

Product **214** arose from 5-*exo* radical addition and partial desulphurisation of substrate **213**, which was a precursor used in the synthesis of the bioactive natural compound mappicine ketone.



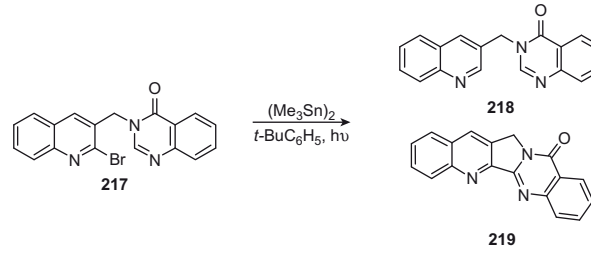
213 214

Scheme 57



215 216

Scheme 58



217 218 219

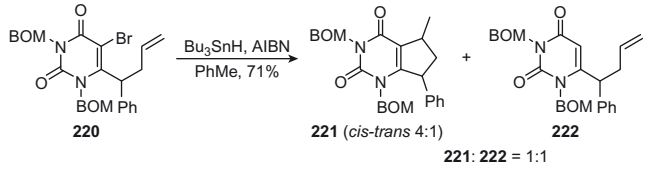
Scheme 59

Following Comins' work (Scheme 54), Hecht (05OL835) accomplished the total synthesis and biological evaluation of 14-aza camtothecin **216** (Scheme 58).

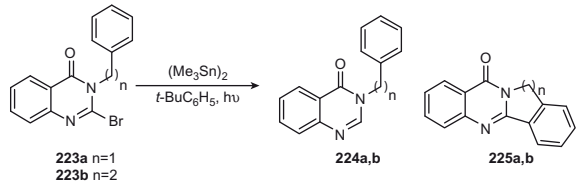
A synthesis of the pentacyclic alkaloid luotonin A **219** *via* a 2-quinolyl radical intermediate has been reported by Bowman (07OBC103). A variety of conditions for the radical cyclisation were explored. Treatment under standard conditions with Bu_3SnH led only to the reduced starting material **218**. Slow addition of the Bu_3SnH gave 14% of luotonin A **219** and 32% of **218** while use of Bu_3GeH gave 18% of luotonin A **219** and 11% of reduced product **218**. The use of $(Me_3Sn)_2$ at reflux in *t*-butylbenzene and with sunlamp irradiation gave luotonin A **219** in 51% yield along with 15% of **218** (Scheme 59).

6. OTHER HETEROAROMATIC RADICALS

While the above examples highlight the synthetic utility of pyridyl, indolyl, thienyl and quinolyl radicals, there are few reports on other



Scheme 60



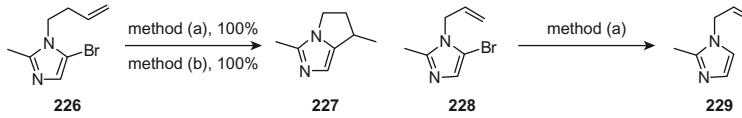
Scheme 61

heteroaromatic radicals. Allen (77JCS(P1)621) describes the generation (under photochemical conditions) and reaction of 5-pyrimidyl radicals with aromatic and heteroaromatic solvents. Subsequent to this, Pedersen (03OBC2908) reported a reaction of a 5-pyrimidyl-derived radical with a terminal alkene (Scheme 60).

The desired cyclised product **221** was isolated as an inseparable 1:1 mixture with reduction product **222**. However, a reasonably good ratio of *cis–trans* was also found (4:1).

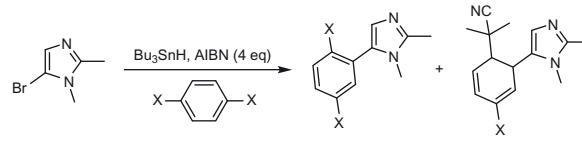
Bowman has reported the use of quinazolinyl radicals in the synthesis of a range of tri- and tetracyclic alkaloids (07OBC103). He explored several radical-based routes to annulate quinazolinone, one of them involving a 2-quinazolinyl radical intermediate. Reaction of 3-benzyl-2-bromo-4-quinazolinone **223a** with Bu_3SnH and Bu_3GeH gave only the reduced product **224a** (Scheme 61) despite the slower rate of hydrogen atom transfer from the germanium hydride. The use of $(Me_3Sn)_2$ at reflux in *t*-butylbenzene and with sunlamp irradiation gave the **224a** in 41% yield along with a 27% yield of the tetracycle **225a**. The phenethyl homolgue **223b** cyclised under the same conditions to give a 97% yield of the tetracyclic **225b**. These results clearly indicate the problem of strain in the 5,6-fused ring system formed during the cyclisation to give **225a**, which is not present in the cyclisation of **223b**. They also demonstrate the 'oxidative cyclisation' process in which the initial cyclohexadienyl radical formed by addition to the phenyl ring is oxidised to give the aromatic product (07CSR1803) (Scheme 61).

An example of the use of the 5-imidazolyl radical has been described by Bowman (90JCS(P1)919). Radicals were generated from the respective halo derivatives, using either an electron-transfer method (Na in NH_3:*t*-BuOH)



(a) Bu_3SnH (1.03 eq), AIBN, PhMe, irradiation.
(b) Na,NH_3, *t*-BuOH.

Scheme 62



Scheme 63

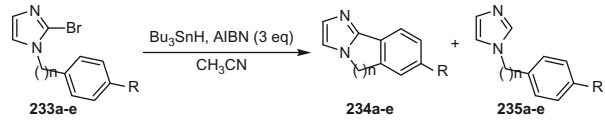
or the more usual Bu_3SnH methodology. Interestingly, from a synthetic point of view, the same paper described the reaction of a suitable molecule **226** under the usual tin-mediated radical conditions, to give a quantitative yield of the 5-*exo*-trig product **227**. No 6-*endo*-trig or reduced products were observed. The same result occurred when **226** was reacted under electron-transfer conditions (Na in NH_3:*t*-BuOH). Again, a quantitative yield of the 5-*exo*-trig product **227** was found. However, shortening the alkyl chain on the imidazolyl nitrogen **228**, gave only reduced **229**. No *exo*- or *endo*- cylisation products were observed (Scheme 62).

Aldabbagh (04T8065) studied the intermolecular radical addition of 5- and 2-imidazolyl radicals to different aromatic solvents, and an example is outlined in Scheme 63.

Among the results of addition to aromatic solvents, particularly interesting is the isolation and characterisation of **232a** from addition of the 5-imidazolyl radical to benzene. This product proved to be stable at the temperature at which the reaction was run, but gave aromatised product **231a** on heating at higher temperatures (increasing the overall yield of **231a** to 60%). The large amounts of AIBN (4 equiv.) used in the protocol accounts for the formation of this side product. From the same author (06OBC268), the utility of the 2-imidazolyl radical in intramolecular cyclisations was demonstrated (Scheme 64).

In this work, intramolecular radical addition to aromatic rings was accomplished, using the common Bu_3SnH-AIBN method or *via* simple irradiation of the radical substrate, which generally gave better results. Irradiation of **233a–e** (2-bromo derivatives) required longer times and resulted in lower conversions, while iodo derivatives **236a–f** proved to be

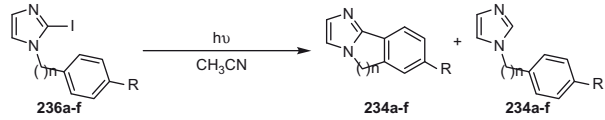
Chemically-induced radical cyclisations:



233a-e **234a-e** **235a-e**

Entry	Starting Material	234	235
1	**233a**, R=H, n=1	–	**a**(45%)
2	**233b**, R=H, n=2	**b**(35%)	**b**(26%)
3	**233c**, R=H, n=3	–	**c**(65%)
4	**233d**, R=F, n=2	**d**(32%)	**d**(19%)
5	**233e**, R=Cl, n=2	**e**(20%)	**e**(31%)

Photochemically-induced radical cyclisations:



236a-f **234a-f** **234a-f**

Entry	Starting Material	234	235
1	**236a**, R=H, n=1	–	**a**(45%)
2	**236b**, R=H, n=2	**b**(70%)	–
3	**236c**, R=H, n=3	**c**(48%)	–
4	**236d**, R=Cl, n=2	**d**(66%)	**d**(19%)
5	**236e**, R=CF_3, n=2	**e**(53%)	**e**(31%)
6	**236f**, R=NO_2, n=2	**f**(32%)	–

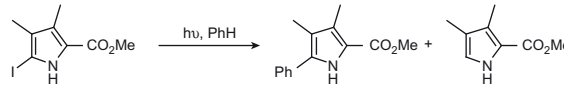
Scheme 64

better substrates. When *n*=1, no cyclisation product was found using either method, while for *n*=2, the photochemically induced reactions proved to be more effective. The decrease in yields, when an electron-withdrawing group was present on the aromatic ring, was explained by the electrophilic nature of the initial 2-imidazolyl radical. Finally, the 7-membered heterocycle (*n*=3) was formed only under irradiation.

In one of the rare examples of the use of pyrrolyl radicals, Merz (99AGE1442) achieved dimerisation of 2-iodo-3,4-dimethoxy-5-phenyl pyrrole using high temperatures in the presence of copper. D'Auria (97H(45)1775) studied the photochemical behaviour of 2-iodopyrrole derivative **237** in benzene (Scheme 65).

The reaction produced a 1:1 mixture of arylated and dehalogenated **238** and **239**. Knight (99TL6117) also used a 3-pyrrolyl radical in this synthesis of the roseophilin core (Scheme 66).

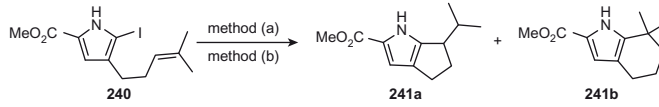
The standard tin hydride method gave a 65% yield of the expected 5-*exo*-trig **241a**; however, TTMSS gave a surprising result, leading to a 1:1



237 **238** **239**

238: 239=1:1

Scheme 65

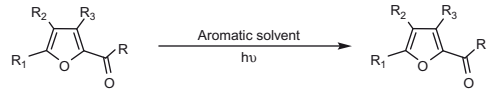


240 **241a** **241b**

(a)Bu_3SnH, AIBN, PhH, reflux, 65% (**241a**)

(b)TTMSS, AIBN, PhH, reflux, 1:1 (**241a:241b**)

Scheme 66



242 **243**

Entry	Starting Material	Product
1	**242a**, R=H, R_1=Br, R_2=R_3=H	**243a**, R=H, R_1=Ar, R_2=R_3=H
2	**242b**, R=H, R_1=R_2=H, R_3=Br	**243b**, R=H, R_1=R_2=H, R_3=Ar
3	**242c**, R=H, R_1= R_3, R_2=Br	**243c**, R=H, R_1= R_3, R_2=Br
4	**242d**, R=H, R_1=R_2=Br, R_3=H	**243d**, R=H, R_1=Ar, R_2=Br, R_3=H
5	**242e**, R=CH_3, R_1=R_2=Br, R_3=H	**243e**, R=CH_3, R_1=Ar, R_2=Br, R_3=H

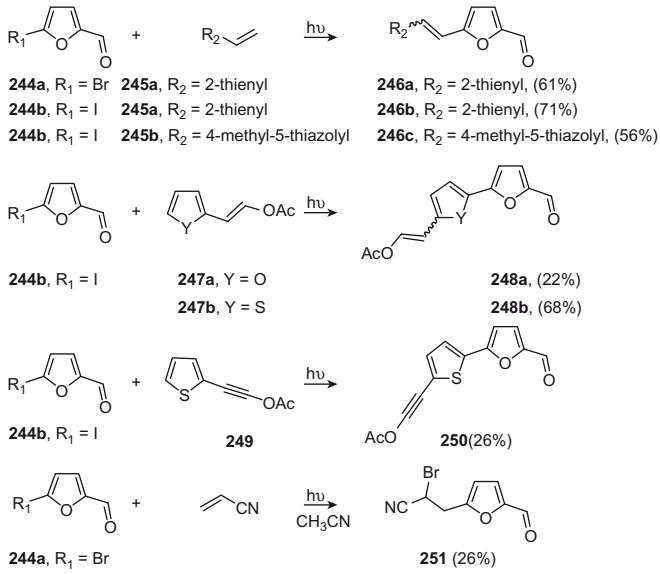
Ar= phenyl, 2,5-dimethylphenyl, 2,4-dimethylphenyl, 2-tolyl, 4-tolyl, 2-furyl, 5-methyl-2-furyl, 2-naphthyl, yields=31–75%.

Scheme 67

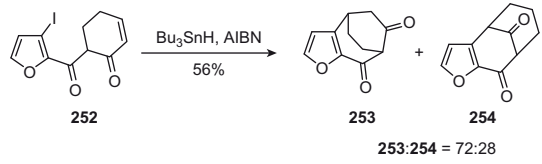
mixture of the expected **241a** and the product of the 6-*endo*-trig cylisation **241b**. The use of a slower *H*-donor (TTMSS) presumably allowed the rearrangement to occur, yielding the thermodynamically more stable 6-membered ring.

An extensive study on the photochemical behaviour of furyl radicals in the presence of aromatic solvents and olefins was reported by D'Auria (85T3441, 85JCS(P1)1285, 86JCS(P1)1755) (Scheme 67).

In this example (85T3441, 85JCS(P1)1285, 86JCS(P1)1755), arylation of furans was successfully achieved by irradiation of bromofuran derivatives **242a–e** in aromatic solvents. The 4-bromofuran derivative **242c** was inert under the conditions used and the 3,5-dibromo derivatives **242d** and **242e** afforded arylation only at the 5-position. In Scheme 68 (90JOC4019, 94JCS(P1)1245, 99T2013), intermolecular addition to alkenes is described.



Scheme 68



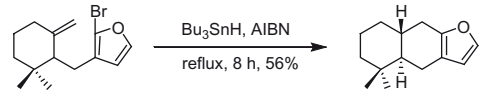
Scheme 69

Changing the electronic nature of the vinyl aromatic coupling partner from **235a,b** resulted in a shift in the regiochemistry from addition to the C═C bond to addition to the aromatic ring in the case of **247a**. Use of acetonitrile, gave haloarylation of the alkene to give **251** in 26% yield. In a similar manner, Duffault (98SC2467) performed the radical addition of a 3-furyl radical onto a C═C bond. The major product **253** was derived from a 7-*endo* cyclisation (Scheme 69).

Following the work presented in Scheme 69, Ray (05SL1951) used a furyl radical for the synthesis of the glaucescenolide analogue **256** (Scheme 70).

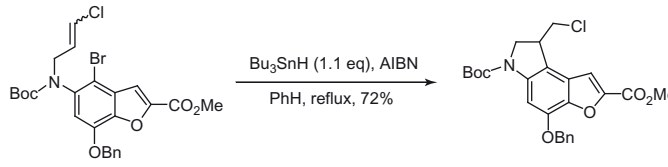
Patel (97JOC8868) has used a 4-benzofuryl radical for the synthesis of *seco*-(+)-oxaduocarmycin SA (LY307918), an analogue of (+)-duocarmycin SA (Scheme 71).

The 5-*exo*-trig cylisation product **258** was the sole material isolated in 72% yield. In a similar attempt to synthesise new duocarmycin



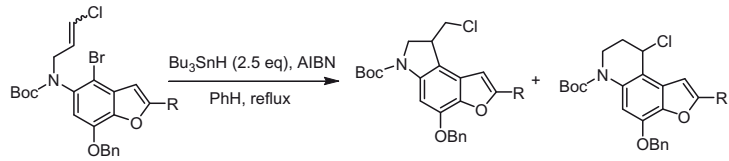
255 **256**

Scheme 70



257 **258**

Scheme 71

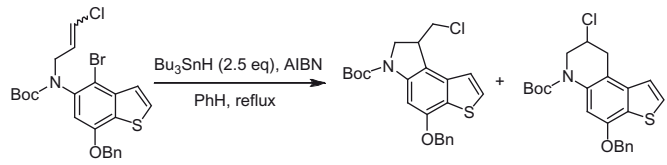


259a, R=H
259b, R=CH_3

260a(40%)
260b(37%)

261a(48%)
261b(32%)

Scheme 72



262

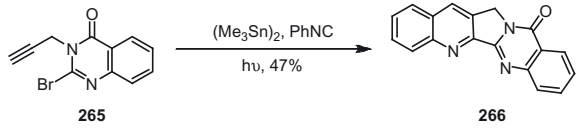
263 (35%)

264 (32%)

Scheme 73

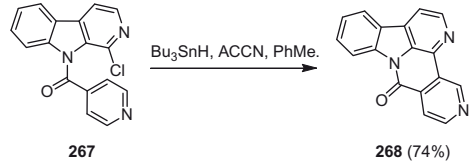
analogues, Lee (04MOL125) carried out a radical addition of a 4-benzofuryl radical onto an alkene (Scheme 72).

Products of 5-*exo* cyclisation **260a** and **260b** were obtained along with a considerable amount of the 6-membered **261a** and **261b**, which can arise from a direct 6-*endo*-cyclisation process or *via* rearrangement of the radical intermediate from the 5-*exo* cyclisation. In the same paper a 4-benzothienyl radical was used for the same purpose with similar results (04MOL125) (Scheme 73).



265 266

Scheme 74



267 **268** (74%)

269 **270** (21%)

Scheme 75

Alvarez-Builla (02SL1093) presented the only example of 2-pyrazinyl radical, describing its addition to a pyridine ring, in a peculiar radical addition–rearomatisation reaction, also described for pyridyl radicals (Scheme 17). On the basis of the work developed during the camptothecin project (Scheme 54), Curran reported the synthesis of the natural alkaloid luotonin A (05SL2843), employing a 2-quinazolinonyl radical (Scheme 74).

Analogous to Scheme 23, Markgraft (05T9102) also described addition of a carbazole and an azacarbazole radical to a pyridine ring to produce cyclised **268** and **270** in good yield (Scheme 75).

7. SUMMARY

Over the past few decades, the importance and strategic relevance of aryl radicals in synthesis has been clearly recognised by the number of reviews. However, the corresponding heteroaryl radicals have not received the same recognition despite their potential, which this review has highlighted. The wide-ranging nature and use of heteroaryl radicals clearly illustrate their comparable importance, particularly when the biological relevance of the products is taken into consideration.

LIST OF ABBREVIATIONS

ACCN	1,1′-azobis(cyclohexanecarbonitrile)
AIBN	2,2′-azobis(2-methylpropionitrile)
BOM	benzyloxymethyl
equiv.	equivalents
ewg	electron withdrawing group
MCB	monochlorobenzene
NMDA	*N*-methyl-D-aspartic acid
PMHS	poly(methylhydroxysiloxane)
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TMS	trimethylsilyl
TTMSS	tristrimethylsilylsilane
TS	*para*-tolunesulphonyl

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CHAPTER 5

Dialkyl Acetone-1,3-Dicarboxylates and their Mono- and *bis*(Dimethylamino) methylidene Derivatives in the Synthesis of Heterocyclic Systems

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1. INTRODUCTION

Heterocyclic chemistry represents a broad and important research field of interest for academic, as well as for industrial, pharmaceutical and phytopharmaceutical areas. The remarkable activity in this field is demonstrated by the great number of contributions devoted to their fundamental properties, and dealing with their applications in medicinal chemistry and material sciences. Therefore, the development of new strategies of preparation is of considerable interest.

We investigated the versatility of 2-substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones. They are enamino masked analogues of β-keto aldehydes and, like their parent 1,3-dicarbonyl compounds, are versatile reagents in the preparation of heterocyclic systems (for reviews see: 04CR2433, 00SL1077, 00MI105) and enaminones have been widely used as key intermediates in the synthesis of functionalized heterocycles (06ARKIVOC(vii)35, 04MC629, 02JHC437, 08TA330, 08AJC107, 07TA2746, 07TA2365, 07T11213) and natural product analogues (05MI211, 08T2801, 06HCA240, 07TA464, 08T2801, 08S1436) as well as in combinatorial applications (03ARKIVOC(xiv)37, 03S1025, 04JCC356, 06JCC95, 07JCC219, 08JCC664). In this review we demonstrate the usefulness of dialkyl acetone-1,3-dicarboxylates and their (dimethylamino)methylidene derivatives as versatile building blocks in the construction of many five- and six-membered heterocyclic systems, and their fused analogues (Figure 1).

2. TRANSFORMATIONS OF DIALKYL ACETONE-1,3-DICARBOXYLATES AND THEIR (DIMETHYLAMINO) METHYLIDENE DERIVATIVES

There are many methods for the synthesis of pyrazoles (02SOS(12)15, 84CHEC(5)167, 96CHEC-II(3)1, 08CHEC-III(4)1).

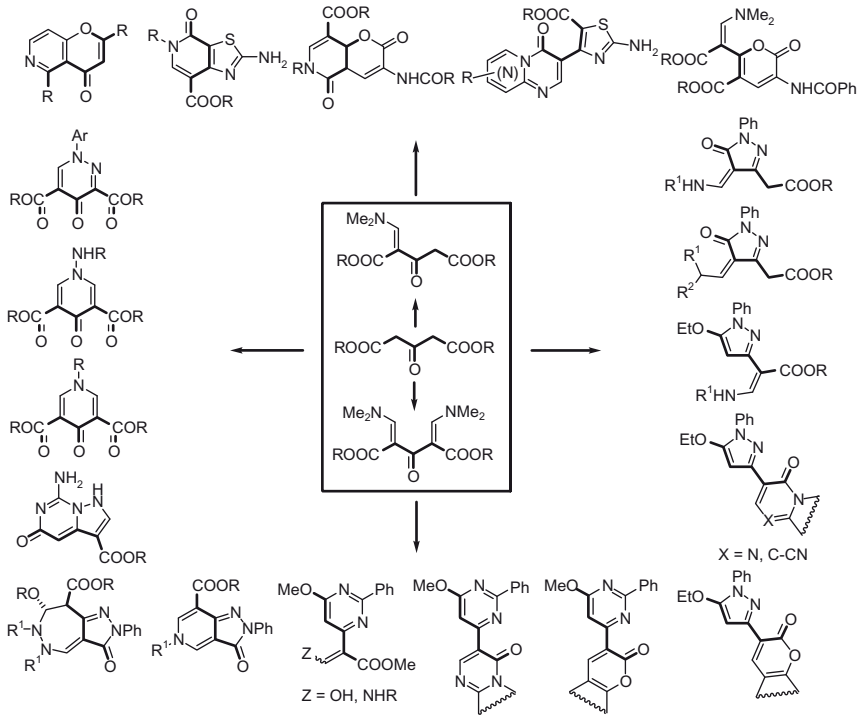
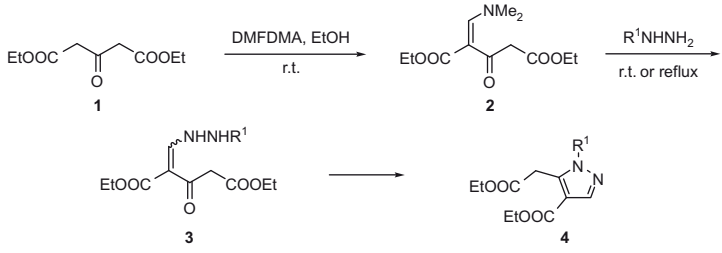


Figure 1 Heterocycles obtained from dialkyl acetone-1,3-dicarboxylates and their (dimethylamino)methylidene derivatives.

2.1 Synthesis of 1-substituted 4-ethoxycarbonyl-5-(ethoxycarbonylmethyl)pyrazoles

Diethyl acetone-1,3-dicarboxylate (**1**) reacts with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in ethanol at room temperature to give diethyl 1-dimethylamino-3-oxobut-1-ene-2,4-dicarboxylate (**2**), which was used without isolation and purification. To this mixture 1 equivalent of a monosubstituted hydrazine was added and then stirred at room temperature or heated under reflux for several hours to form intermediates **3**, which were, without isolation, cyclized into 1-substituted 4-ethoxycarbonyl-5-(ethoxycarbonylmethyl)pyrazoles **4** in 24–71% yield (08ACSi1019) (Scheme 1).

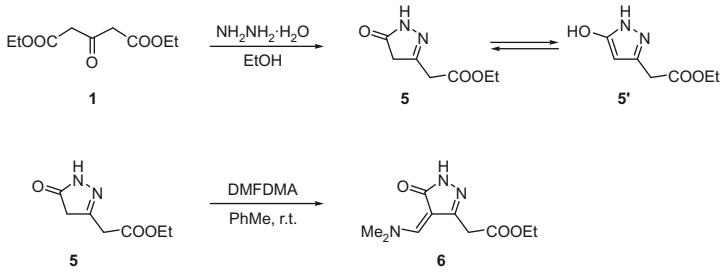
Ethyl 2-(4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)acetate (**5**), prepared from diethyl acetone-1,3-dicarboxylate (**1**) and hydrazine hydrate in ethanol at room temperature, was transformed with DMFDMA in toluene at room temperature into ethyl (*Z*)-2-{4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acetate (**6**) in 76% yield (07H657) (Scheme 2).



1 2 3 4

R^1 = Me, $PhCH_2$, pyrid-2-yl, pyrimidin-2-yl, 6-chloro-pyridazin-3-yl, 6-Ph-pyridazin-3-yl, imidazo[1,2-*b*]pyridazin-6-yl

Scheme 1



1 5 5' 6

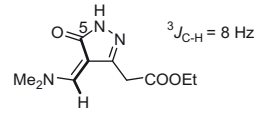
Scheme 2

The structure of **6** was determined by HMBC 2D NMR. Spectral data gave the coupling constant between the C(5) carbon atom and the methylidene proton, $^3J_{C-H} = 8$ Hz, thus indicating *trans* orientation of the methylidene proton and the carbonyl group around the exocyclic double bond or (*Z*)-configuration around the exocyclic double bond (Figure 2).

In the reactions of **6** with *N*- and *C*-nucleophiles in ethanol at room temperature and an equimolar amount of hydrochloric acid, the dimethylamino group was substituted to give **7** and **8** in 61–80% yields, respectively. Since **6** is soluble in water with hydrochloric acid, the reactions can also be carried out in water with essentially the same yields, as the corresponding reactions in ethanol, with simple isolation of the products (Scheme 3).

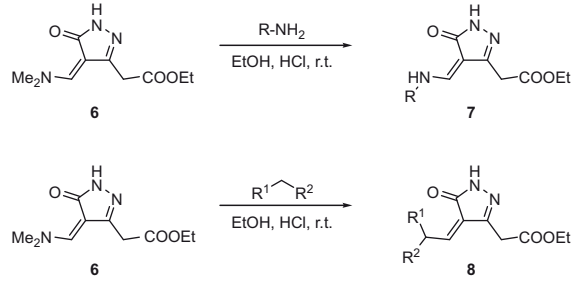
Compound **6** reacts with DMFDMA in boiling DMF to give ethyl (*E*)-3-(dimethylamino)-2-{(*Z*)-4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}propenoate (**9**) in 70% yield. Fortunately, annular *N*-methylation did not take place (Scheme 4).

The structure of **9** was determined on the basis of its HMBC 2D NMR. Spectral data gave coupling constants $^3J_{C-H} = 8$ Hz and $^3J_{C-H} = 5$ Hz, thus indicating (*Z*)-orientation around the exocyclic double bond and



6

Figure 2 The structure of 6 determined by HMBC 2D NMR.

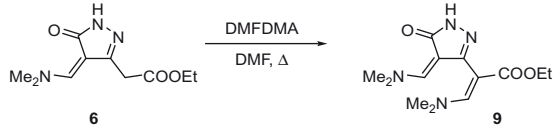


6 **7** **8**

R = CH_2CH_2COOEt (51%); 4-nitrophenyl (90%), 4-bromophenyl (77%), 4-methylphenyl (79%)

R^1CHR^2 = 6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl (66%)
6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl (80%)
3-hydroxy-1-oxo-1H-inden-2-yl (66%)
5-hydroxy-1,3-diphenyl-1H-pyrazol-4-yl (61%)

Scheme 3



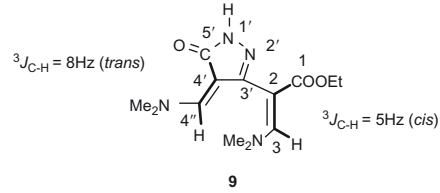
6 **9**

Scheme 4

(*E*)-orientation on the side chain attached at the 3′-position, respectively (Figure 3). These configurations are in agreement with previously observed configurations in 1-phenyl-substituted analogues.

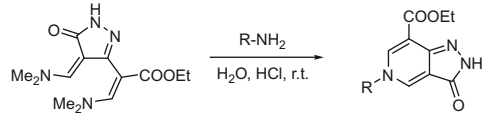
2.2 Synthesis of pyrazolo[4,3-*c*]pyridine derivatives

Since **9** was soluble in water, its reactions with primary amines were carried out in aqueous hydrochloric acid at room temperature, to precipitate pyrazolo[4,3-*c*]pyridines **10** after 12 h in good yields and in analytical purity (Scheme 5).



9

Figure 3 The structure of 9 determined by HMBC 2D NMR.



9 **10**

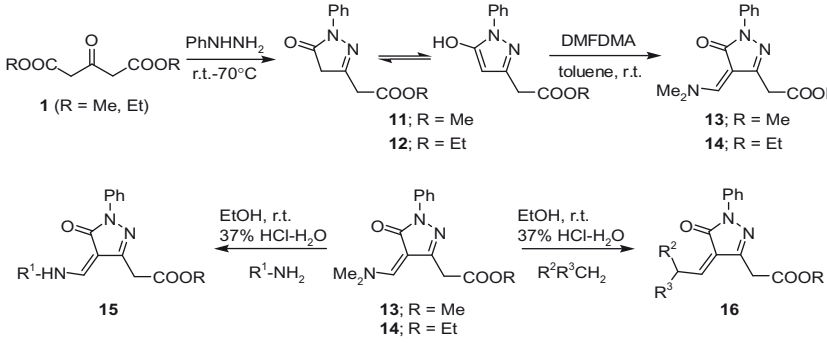
R = Me; CH_2CN; quinolin-3-yl

Scheme 5

2.2.1 Transformation of alkyl (5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)acetates into 5-heteroaryl-3-oxo-2-phenyl-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates (03H197)

There are only a few methods for the preparation of pyrazolo[4,3-*c*] pyridines starting from substituted pyrazoles (84CHEC(5)305, 96CHEC-II(7)283, 08CHEC-III(10)431). Other methods involve an aza Wittig-type reaction starting from 5-formyl-1-phenylpyrazole (91T6737), intramolecular cycloaddition of azomethine imines (70TL3091), ring opening of pyrido[4,3-*d*]pyrimidine derivatives with sodium methoxide followed by rearrangement and cyclization (74JHC163), photochemical irradiation of 4-hydrazino-isoxazolo[5,4-*b*]pyridines (88H1899), cyclization of diazonium salts generated from 5-alkyl-4-amino-2-trifluoro-methylpyridines (01T2051), nitrosation of *N*-acylated 4-amino-3-methylpyridines (94USP5300478), treatment of piperidones with hydrazines, which afforded 1,4,5,6-tetrahydropyrazolo[4,3-*c*]pyridines (02H257), treatment of (*E*)-1-methyl-3,5-*bis*(4-methylbenzylidene)-4-piperidone, and analogues with hydrazines (00JMC2915), from 4-amino-5-methylnicotic acid (57AP494) and from *N*-substituted 4-pyridone benzoylhydrazones (58LA181). 5-Alkoxy-3-(*N*-substituted carbamoyl)-1-phenylpyrazoles were tested for anti-inflammatory and hypnotic activity (77JMC80).

Compounds **11** and **12** were transformed with DMFDMA in toluene at room temperature into methyl [(*Z*)-4-(dimethylamino) methylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate (**13**) and ethyl ester (**14**). They reacted with *N*- and *C*-nucleophiles in ethanol with hydrochloric acid at room temperature to give dimethylamine



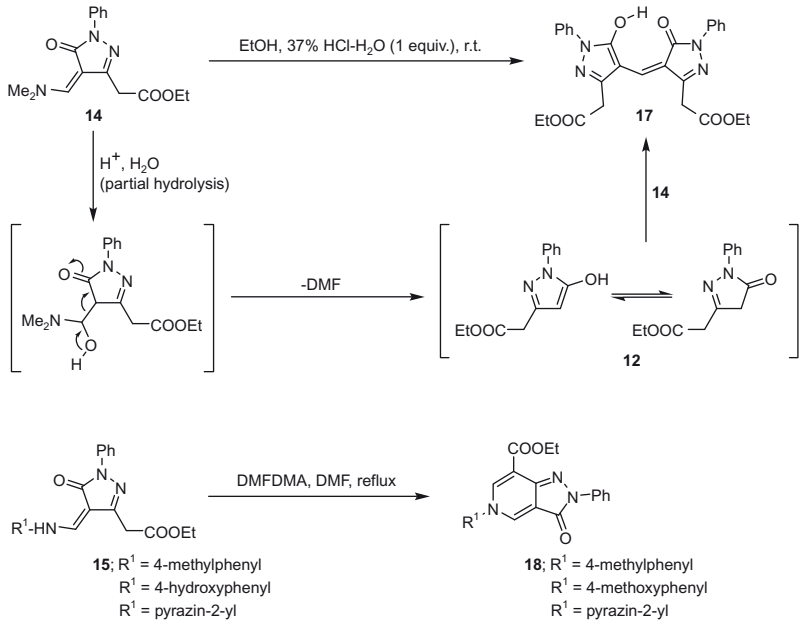
Scheme 6

substitution products **15** and **16**. In the *N*-nucleophile series, aromatic and heterocyclic amines were used. The corresponding methyl and ethyl (*Z*)-[5-oxo-1-phenyl-4-(hetero)arylaminomethylidene-4,5-dihydro-1*H*-pyrazol-3-yl]acetates **15** were produced. In the IR spectra of **15** (R=Me, Et; R^1=CH_2CN), obtained from **13** and **14** and aminoacetonitrile, there was no absorption between 2100 cm^{-1} and 2200 cm^{-1}, characteristic for the C≡N group. At first, we thought that cyclization occurred to give alkyl (7-imino-1-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*f*][1,4]oxazepin-3-yl)acetates. However, the X-Ray analysis showed that **15** (R=Me, Et; R^1=CH_2CN) exist in the cyano form. Reactions with *C*-nucleophiles proceeded under the same conditions to form **16** in 57–98% yield (Scheme 6).

When **14** was heated in ethanol under reflux with hydrochloric acid, (*Z*)-[4-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethylidene)-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate (**17**) was obtained in 75% yield, identical with the compound prepared from **14** and **12** in 90% yield. Apparently, partial hydrolysis of enamine **14** took place to furnish *in situ* pyrazole **12**, which reacted as the *C*-nucleophile with the non-hydrolysed enaminone **14** to afford **17**. Compounds **15** were heated with 2 equivalents of DMFDMA in DMF under reflux to give pyrazolo[4,3-*c*] pyridines **18** in moderate yields. Cyclization proceeds by incorporation of DMFDMA as a C_1 synthon between the nucleophilic NH and CH_2 groups. In the reaction of **15** (R^1=4-hydroxyphenyl) with DMFDMA, methylation of the phenolic hydroxy group also took place to give the 5-(4-methoxyphenyl)pyrazolo[4,3-*c*]pyridine (**18**; R=4-methoxyphenyl) (Scheme 7).

Conformations of key structures were determined by HMBC 2D NMR and/or observed nuclear Overhauser effects between selected protons (Figure 4).

Compound **19** was prepared from ethyl (5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**12**) and 2 equivalents of DMFDMA in DMF in



Scheme 7

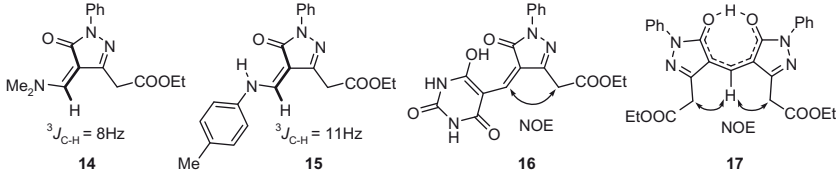
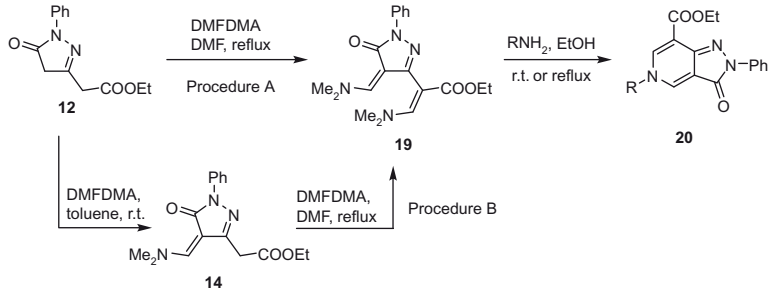


Figure 4 Conformations of key structures determined by HMBC 2D NMR and/or nuclear O. e.

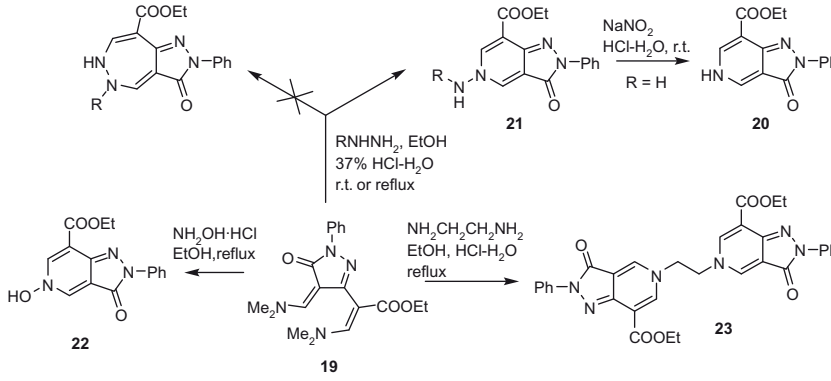
53% yield (Procedure A). Alternatively, **19** was also obtained on treatment of (*Z*)-(4-dimethylaminomethylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**14**) and 1.3 equivalents of DMFDMA in DMF in 56% yield (Procedure B). When **19** was treated with ammonia, alkylamines and (hetero)arylamines in ethanol at room temperature or under reflux, it formed ethyl 3-oxo-2-phenyl-3,5-dihydro-2*H*-pyrazolo [4,3-*c*]pyridine-7-carboxylate (**20**; R=H) and its 5-substituted derivatives **20** (R≠H) (Scheme 8).

Treatment of **19** with hydrazine and monosubstituted hydrazines in ethanol at room temperature or under reflux gave 5-amino- **21** (R=H) and 5-aminosubstituted pyrazolo[4,3-*c*]pyridine-7-carboxylates **21** (R≠H), while with hydroxylamine hydrochloride the corresponding 5-hydroxy derivative **22** was formed in 82% yield. Nitrosation of **21** (R=H) with



R = H, Me, Pr, *n*-Bu, cyclohexyl, benzyl, 4-methoxybenzyl, 4-nitrobenzyl, 2-(5-methyl-1*H*-indolyl-3)ethyl, (1-adamantyl)ethyl, CH_2CH_2COOEt, CH_2COOEt, MeOTyr (*S*), EtOAla (*S*), CH_2CN, Ph, 4-methylphenyl, 4-methoxyphenyl, pyrazin-2-yl, pyridin-2-yl, quinolin-3-yl, 1,3-benzothiazol-2-yl, tetrazol-5-yl, 5-methylisoxazol-3-yl

Scheme 8



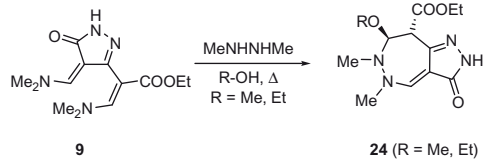
R = 2-bromophenyl, 2-chlorophenyl, pyridin-2-yl, phthalazin-1-yl

Scheme 9

sodium nitrite in aqueous hydrochloric acid afforded the deamination product **20** (R=H) identical to that obtained on treatment of **19** with ammonia. When **19** was treated with 1,2-ethylenediamine in ethanol under reflux for 2 h 1,2-*bis*(ethoxycarbonyl-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridine-5-yl)ethane (**23**) was isolated in 68% yield (Scheme 9).

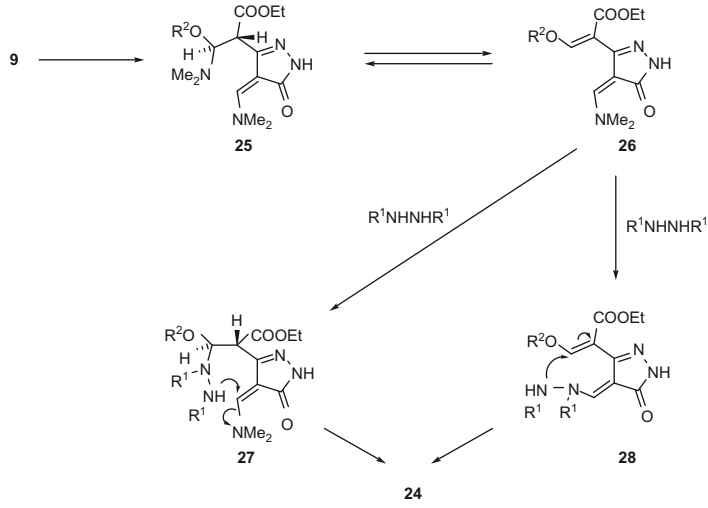
2.3 Synthesis of pyrazolo[4,3-*d*][1,2]diazepine derivatives

While pyrazolo[3,4-*d*][1,2]diazepines have been obtained by cycloaddition of 2-diazopropane to 1,2-diazepines (72TL2851, 74T2851, 80TL4507, 85CB4682, 91T2925, 91JHC369), isomeric pyrazolo[4,3-*d*][1,2]diazepines are mentioned in the literature only once. Namely, in the heterocyclization of 5-acetylenylpyrazole-4-carboxylic acid hydrazides under the



9 **24** (R = Me, Et)

Scheme 10



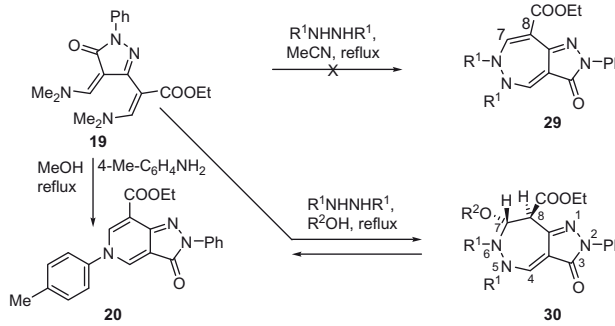
Scheme 11

influence of CuCl, an unexpected formation of a diazepinone and dehydrodimerization into the corresponding *bis*(pyrazolo[4,3-*d*][1,2] diazepinone (05TL4457) occurred.

With 1,2-dimethylhydrazine, **9** reacts on heating in methanol or ethanol under reflux for several hours to give methyl or ethyl 2,3,5,6,7,8-hexahydropyrazolo[4,3-*c*]diazepine-8-carboxylates (**24**; R=Me or Et) (Scheme 10).

The mechanism of the formation of **24** is unknown, however, one possible explanation would be either the formation of aminal **25** or enol ether **26** as intermediates in the presence of an alcohol, followed by a reaction with 1,2-disubstituted hydrazine to form intermediates **27** and **28**, which cyclize into **24** (Scheme 11).

In the reaction of **19** with hydrazine or monosubstituted hydrazines, the corresponding 5-amino-substituted pyrazolo[4,3-*c*]pyridine-7-carboxylates was formed (see Scheme 9). When **19** reacted with 1,2-disubstituted hydrazines in acetonitrile, no cyclization to **29** took place. However, in an alcohol, compounds **30** were formed (Scheme 12,



Scheme 12

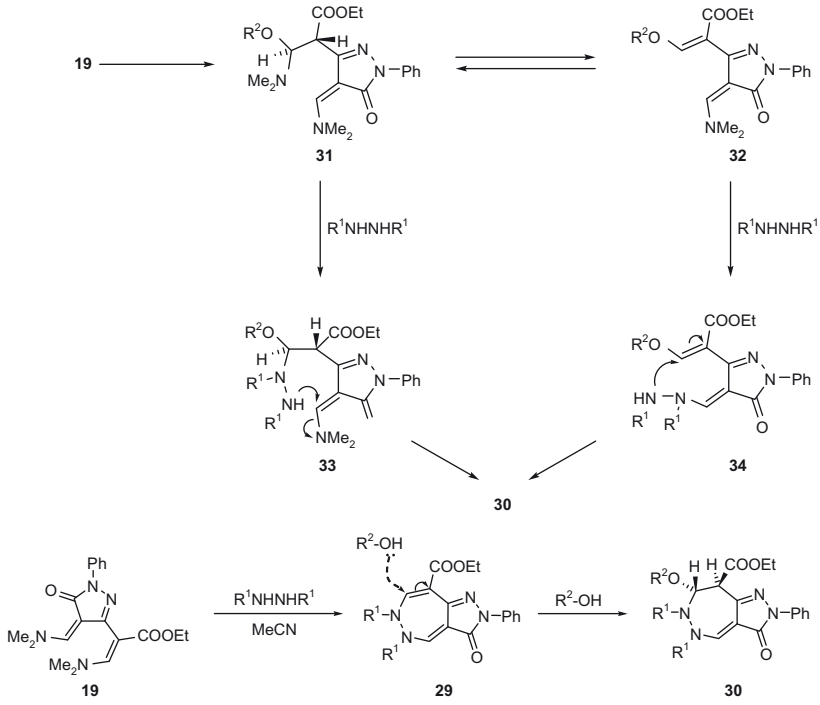
Table 1. Pyrazolo[4,3-*d*][1,2]diazepine derivatives

Compound	R^1	R^2	Reaction time (h)	Yield (%)
30a	Me	Me	1.5	74
30b	Me	Et	1.5	81
30c	Me	*n*-Pr	4	83
30d	Me	*i*-Pr	4	41
30e	Me	*n*-Bu	2	67
30f	Me	*t*-Bu	3	89
30g	Me	Allyl	7.5	59
30h	Et	Me	7	51
30i	Et	Et	7	61
30j	Et	*n*-Pr	7	40
30k	Et	*i*-Pr	7	47

Table 1). The mechanism of formation of **30** is unknown. However, since the cyclization in a non-hydroxylic solvent did not produce the pyrazolo [4,3-*d*][1,2]diazepine **29**, the addition of alcohol to the C_7–C_8 double bond in **29** seems unlikely. The possible explanation is therefore that either an aminal **31** or an enol ether **32** are formed as intermediates in the presence of an alcohol. With a 1,2-disubstituted hydrazine, intermediates **33** or **34** are formed, which cyclize to **30** (06T8126) (Scheme 13).

Compound **30a** (R^1=R^2=Me) was transformed with 4-methylaniline into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate **20**, identical with that prepared previously (Scheme 12, see also Scheme 8).

Substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates **30** were obtained from ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**19**) *via* substitution of both dimethylamino groups



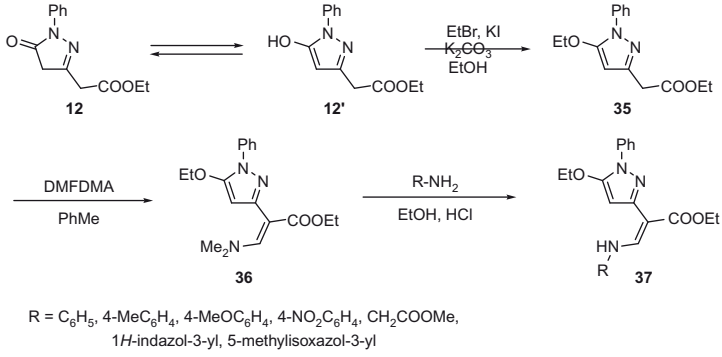
Scheme 13

with 1,2-dialkylhydrazines, and subsequent addition of alcohol to the C_7–C_8 double bond. Pyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates **30** with an amine, gave pyrazolo[4,3-*c*]pyridine-7-carboxylate **20**.

2.4 Synthesis of fused pyrazol-3-yl-pyrimidine derivatives and fused pyrazol-3-yl-pyranones

Ethyl (2*E*)-3-(dimethylamino)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)propenoate (**36**) with various *N*- and *C*-nucleophiles gave ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-(substituted amino)propenoates **37**, fused pyrazol-3-yl-pyrimidinones **38**, **39** and fused pyrazol-3-yl-pyranones **40**, **41** (05H207).

Ethyl (2*E*)-3-(dimethylamino)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl) propenoate (**36**) was prepared in two steps from ethyl (5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (**12**) by treatment with ethyl bromide in ethanol under reflux to give ethyl (5-ethoxy-1-phenyl-1*H*-phenyl-3-yl) acetate (**35**), followed by treatment with DMFDMA in toluene under reflux. Compound **36** reacted with anilines, methyl glycinate hydrochloride, 3-amino-1*H*-indazole and 3-amino-5-methylisoxazol in ethanol in the



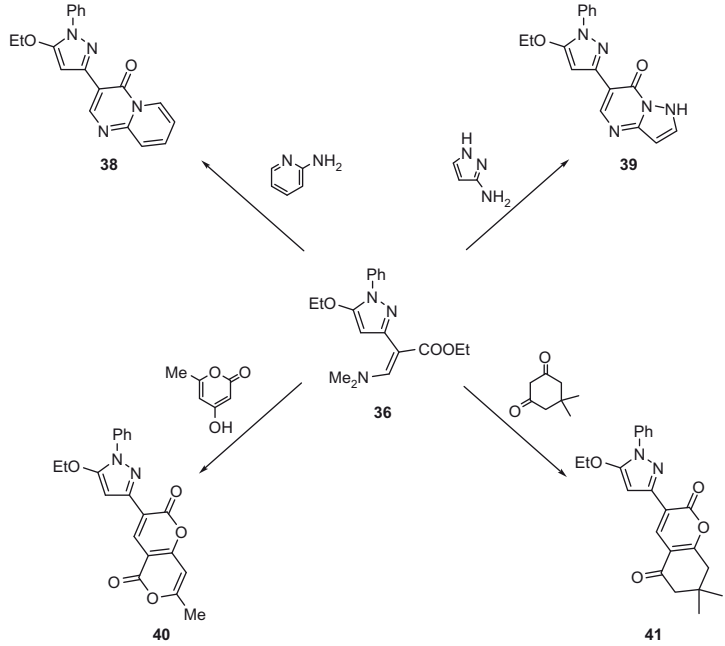
Scheme 14

presence of hydrochloric acid under reflux for 1–3 h to give the corresponding ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-(arylamino)propenoates **37** (Scheme 14).

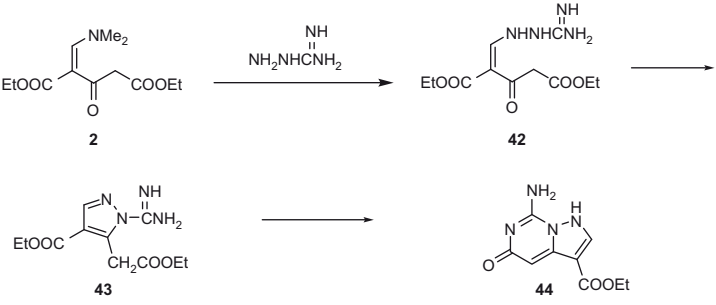
However, when **36** was heated with α-amino heterocycles or with cyclic 1,3-dicarbonyl or potential 1,3-dicarbonyl compounds, 3-heteroarylpyrazol derivatives were obtained. In this manner **36** afforded, when heated with 2-aminopyridine and 3-amino-1*H*-pyrazol in acetic acid under reflux for 2 h and 5 h, respectively, 3-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-4*H*-pyrido[1,2-*a*]pyrimid-4-one (**38**) and 6-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)pyrazolo[1,5-*a*]pyrimid-7(1*H*)-one (**39**) in 70% and 77% yield, respectively. Similarly, **36** afforded with cyclic*β*-dicarbonyl compounds, such as 4-hydroxy-6-methyl-2*H*-pyran-2-one and 5,5-dimethylcyclohexane-1,3-dione by heating in acetic acid for 4 h and 8 h, respectively, the corresponding 3-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (**40**) and 3-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-7,7-dimethyl-7,8-dihydro-2*H*-chromene-2,5-dione (**41**) in 26% and 82% yield, respectively (Scheme 15).

2.5 Synthesis of pyrazolo[1,5-*c*]pyrimidin-5-one derivatives synthesis of 7-amino-3-ethoxycarbonyl-pyrazolo[1,5-*c*] pyrimidin-5(1*H*)-one (08ACSi1019)

There are many methods for the synthesis of pyrazolopyrimidines (02SOS(12)613, 84CHEC(5)305, 96CHEC-II(8)365, 08CHEC-III(11)551). With diethyl 1-dimethylamino-3-oxobut-1-ene-2,4-dicarboxylate (**2**) and aminoguanidine, first a substitution intermediate **42** is formed, which cyclizes into pyrazole **43**, followed by cyclization into the bicyclic 7-amino-2-ethoxycarbonyl-1*H*,2*H*-pyrazolo[2,3-*c*]pyrimidin-5-one (**44**). The intermediates **42** and **43** were not isolated (08ACSi1019) (Scheme 16).



Scheme 15

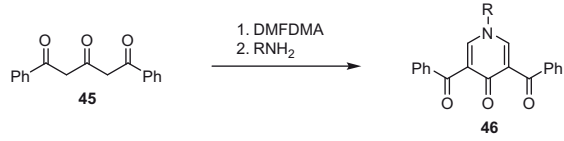


Scheme 16

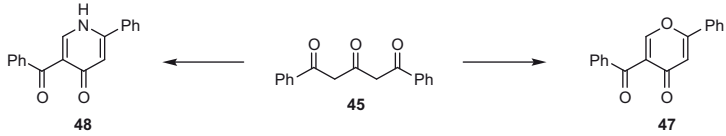
2.6 Synthesis of pyridin-4(1*H*)ones (06H899)

There are several methods for the preparation of 4-oxo-1,4-dihydropyridine derivatives (74B597, 84CHEC(2)395, 96CHEC-II(5)167, 08CHEC-III(7)217).

1,5-Diphenyl-1,3,5-pentanetrione (**45**) with excess of DMFDMA followed by the addition of amines yielded 1-substituted 3,5-dibenzoyl-4-oxo-1,4-dihydropyridines **46** (Scheme 17).



Scheme 17



Scheme 18

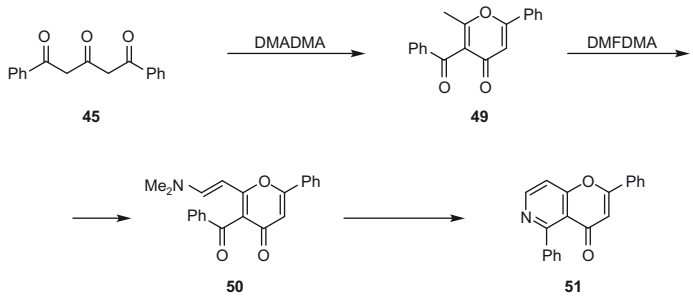
Reaction of 1,5-diphenyl-1,3,5-pentanetrione (**45**) with DMFDMA was carried out in propyl acetate under reflux for 12 h, followed by removal of the solvent by vacuum distillation. The oily residue was dissolved in another solvent (usually ethanol) and cyclization with various amines under reflux in the presence of catalytic amounts of concentrated hydrochloric acid was performed to form 1-substituted 3,5-dibenzoyl 4-oxo-1,4-dihydropyridines (**46**) (Scheme 17).

1-Substituted 3,5-dibenzoyl 4-oxo-1,4-dihydropyridines (**46**) are crystalline compounds with high melting points. They were isolated by direct crystallization from the reaction in high yields.

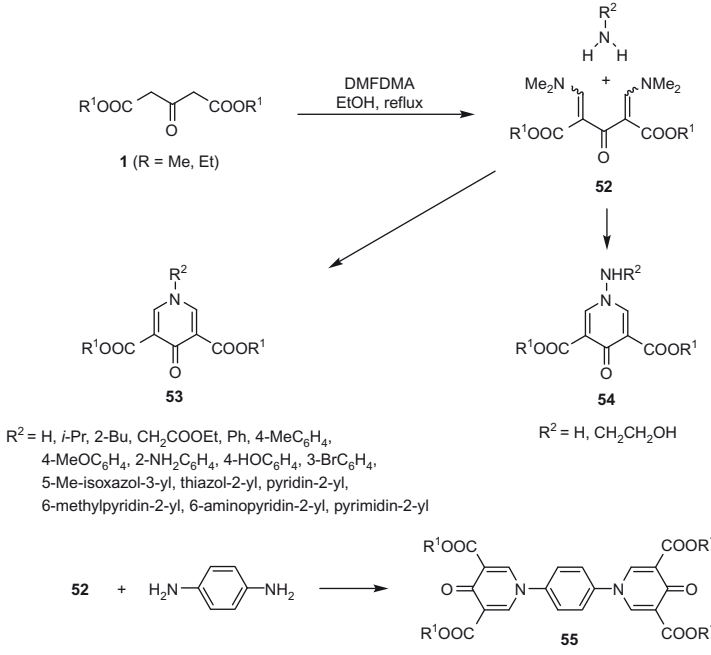
1,5-Diphenyl-1,3,5-pentanetrione (**45**) has proved successful in other conversions with DMFDMA. When 1,5-diphenyl-1,3,5-pentanetrione (**45**) reacted only with 1 equivalent of DMFDMA, the isolated product was pyranone **47** (Scheme 18). The structure of **47** was confirmed by single crystal X-ray analysis.

1,5-Diphenyl-1,3,5-pentanetrione (**45**) was successfully used for the preparation of pyridone **48**. 5-Benzoyl-2-phenyl-4(1*H*)pyridone (**48**) was prepared from 1,5-diphenyl-1,3,5-pentanetrione (**45**) with 1 equivalent of DMFDMA in propyl acetate at room temperature followed by NH_4Cl. The product precipitated from the mixture. But the synthesis of *N*-substituted pyridones was not successful (Scheme 18).

1,5-Diphenyl-1,3,5-pentanetrione (**45**) with 1 equivalent of *N*,*N*-dimethylacetamide dimethyl acetal (DMADMA) yielded 5-benzoyl-2-phenil-6-methyl-4-pyranone (**49**). Pyranone **49** with DMFDMA yielded **50**, which was converted to 2,5-diphenyl-1*H*,4*H*-pyrido[4,3-*b*]pyrane-4-one (**51**) by cyclization of compound **50** with aqueous ammonia. This reaction was performed in DMF at 80 °C and the product precipitated from the mixture (Scheme 19).



Scheme 19



Scheme 20

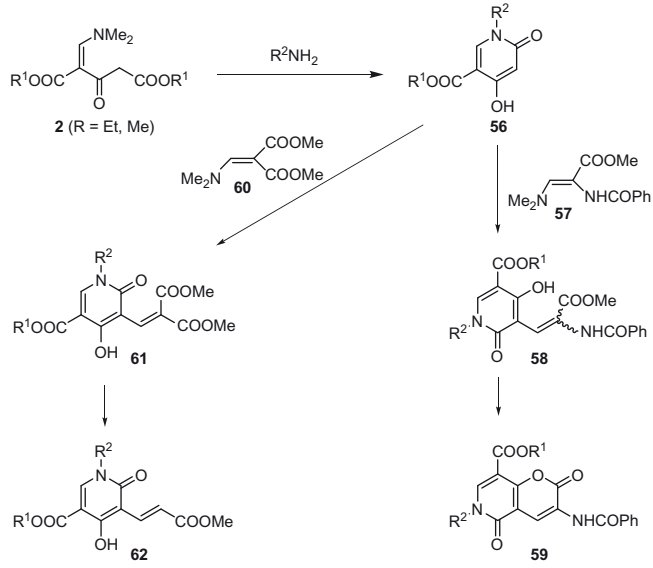
Dialkyl acetone-1,3-dicarboxylates **1** were transformed with DMFDMA by heating in ethanol into dialkyl 1,5-*bis*(dimethylamino)-3-oxo-penta-1,4-diene-2,4-dicarboxylates **52** in good yields. They were treated with ammonia, hydrazine, primary aliphatic, aromatic or heterocyclic amines to form dialkyl 1-substituted 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates **53** and **54**. 1,4-Diaminobenzene reacts with **52** in a 1:2 molar ratio to produce 1,4-*bis*[3,5-*bis*(alcoxycarbonyl)-4-oxo-1,4-dihydropyridin-1-yl]benzene **55** in 57% yield. Hydrazine and monosubstituted hydrazines afforded 1-amino-1,4-dihydro-4-oxopyridines **54** (00H2033) (Scheme 20).

2.7 Synthesis of 4-hydroxypyridin-2(1*H*)-one and pyrano[3,2-*c*] pyridinone derivatives

2.7.1 The synthesis of 4-hydroxypyridin-2(1*H*)-ones (**56**) and 6-substituted 3-benzoylamino-2,5-dioxo-5,6-dihydro-2*H*-pyrano [3,2-*c*]pyridine-8-carboxylates (**59**) (08ACSi1009)

Many methods for the synthesis of pyrano[3,2-*c*]pyridine derivatives (96CHEC-II(8)345, 02SOS(15)285, 08CHEC-III(7)217) are known.

The dimethylamino group in diethyl (**2**; R=Et) and dimethyl 1-dimethylamino-3-oxobut-1-ene-2,4-dicarboxylates (**2**; R=Me) can be exchanged very easily with nitrogen nucleophiles. With primary amines in methanol or ethanol under reflux for several hours, substitution of the dimethylamino group by an amine takes place followed by intramolecular nucleophilic attack of the amino group on the ester to afford 1-substituted 5-alkoxycarbonyl-4-hydroxypyridin-2(1*H*)-ones **56** in 16–93% yields (Scheme 21). In the reaction of **56** with methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**57**), first the intermediate **58** was formed, which cyclized into 6-substituted 3-benzoylamino-8-ethoxycarbonyl-2*H*,5*H*-pyrido[4,3-*b*]pyran-2,5-diones (**59**). However, with 3-dimethylamino-2-(methoxycarbonyl)propenoate (**60**) intermediate **61** is formed



56: R^1, R^2 = Me, H; Et, H; Me, Me; Et, Me; Et, CH_2CH_2OH; Et, *i*-Pr; Et, Bn; Et, $N(Me)_2$ Et, (phthalazin-1-yl)amino; Et, (4-chlorophthalazin-1-yl)aminio
59: R^1, R^2 = Me, Me; Et, Me; Et, *i*-Pr; Et, $CH_2CH_2OCOCH_3$
62: R^1, R^2 = Me, Me; Et, *i*-Pr

Scheme 21

first. It did not produce a pyranopyridine derivative, instead hydrolysis and decarboxylation of one of the ester groups took place to give 4-hydroxy-5-methoxycarbonyl-1-methyl-3-(2-methoxycarbonyl)ethenyl-pyridin-2(1*H*)-one (**62**) (08ACSi1009) (Scheme 21).

2.8 Synthesis of thiazolo[5,4-*c*]pyridine derivatives

Transformations of ethyl 2-amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate into 5-substituted 2-amino-4-oxo-4,5-dihydrothiazolo[5,4-*c*]pyridine-7-carboxylates 09H2343 in print.

Derivatives of thiazolo[5,4-*c*]pyridines have been prepared previously by cyclization of 2-aminobenzothiol with carboxylic anhydrides (74DE2.330109), by cyclization of *S*-(2-aminoheteroaryl)dithiocarbamates in the presence of a base (88CI302), by cyclization of substituted 4-(2-isocyanatovinyl)thiazole (86JHC1171), and by cyclization of *o*-disubstituted aminopyridines with diethoxymethyl acetate (90JHC563). A review of the preparations of benzothiazoles and related thiazolazines has been published (02SOS(11)835). They show various biological activities (06BMC1309). They are potent inhibitors of factor Xa(fXa) in the blood coagulation cascade (04H1555, 04BMCL2935).

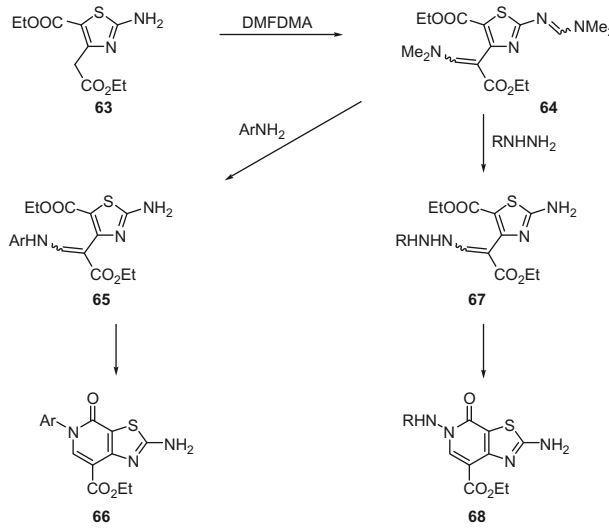
2-Amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate (**63**), prepared from diethyl acetone-1,3-dicarboxylate (**1**) according to the described procedure (74DE2.330109), was transformed with excess DMFDMA into ethyl 4-[1-(dimethylamino)-3-ethoxy-3-oxo-prop-1-en-2-yl]-2-[(dimethylamino)methylideneamino]thiazole-5-carboxylate (**64**). Compound **64** was treated with excess amines in ethanol and catalytic amounts of hydrochloric acid under reflux for several hours. The initial substitution of the *N*,*N*-dimethylaminomethylene group from the amino side chain is followed by cyclization with the ester group at position 5 and elimination of the *N*,*N*-dimethylamino group from the *N*,*N*-dimethylaminomethyleneamine at position 2 of the thiazole ring to give the corresponding 6-substituted 2-aminothiazolo[5,4-*c*]pyridine-4-carboxylates **66** 09H in print (Scheme 22).

6-Aminosubstituted 2-aminothiazolo[5,4-*c*]pyridine-4-carboxylates **68** were isolated from **64** with hydrazines in ethanol and hydrochloric acid (Scheme 22).

2.9 Synthesis of 4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates

2.9.1 Synthesis of dimethyl 1-(hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates from dimethyl 3-oxopentane-1,5-dioates (08ZN863b)407)

There are many syntheses of pyridazines (84CHEC(3)1, 96CHEC-II(6)1, 08CHEC-III(8)1, 97MOS(9a)557, 06SOS(16)125, 05JHC361), because they are important for the preparation of a variety of products in the



66: Ar = C_6H_5, 4-F-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4
68: R = $F_3CCH_2CH_2NH$, C_6H_5NH, 3-Cl-C_6H_4NH, 4-Me-C_6H_4NH, 4-NO_2-C_6H_4NH
6-chloropyridazinyl-3-amino, 6-phenylpyridazinyl-3-amino, pyrimidinyl-2-amino

Scheme 22

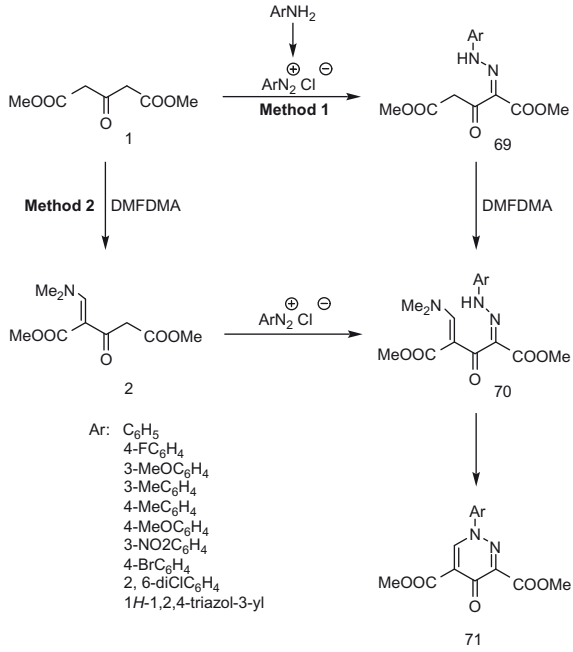
pharmaceutical and the agrochemical fields (01JMC2707, 02T9933, 90M1, 90M141). Also, they are acetylcholinesterase inhibitors (01JMC2707), they act on cardiovascular (02T9933) and inflammatory systems (90M1) and they show antitumour and other activities (90M141). Synthetic transformations on this ring yield diverse analogues for a wide array of applications. They have received new attention with the advent of palladium-catalysed cross-coupling reactions that facilitate the direct introduction of groups onto the pyridazine nucleus *via* carbon–carbon or carbon–heteroatom bond formation (06SL3185).

Despite the widely elaborated [4+2] cycloaddition chemistry of 1,2,4,5-tetrazines, only a few examples of cycloadditions to the exocyclic C=C bonds leading to spirodihydropyridazines are known (75APH237, 00T4213). Recently, [4+2] cycloadditions of 3,6-disubstituted 1,2,4,5-tetrazines to 4′-methylenedihydro-3′H-spiro[bicyclo[2.2.1]heptane-2,2′-furans] and 4′-methylene-1′-(4-nitrophenyl)spiro[bicyclo[2.2.1]heptane-3.2′-pyrrolidine] afforded novel dispirodihydropyridazine derivatives, 11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dienes and 11:14-isopropylidene-11-methyl-2,3,8-triazadispiro[5.1.5.2]pentadeca-1,4-dienes (07TA2746). A one-pot, three-step regio- and stereoselective synthesis of functionalized oxazoline-fused

pyridazines by a base-assisted 'Michael addition-pyridazine cyclization-oxazoline cyclization' cascade reactions of 4-chloro-1,2-diaza-1,3-butadienes with 3-(dimethylamino)prop-2-enoates have been reported (07SL2971). The coupling of dimethyl 3-oxopentane-1,5-dioate (dimethyl acetone-1,3-dicarboxylate) with a variety of aryldiazonium salts where hydrazones are formed, afforded by cyclization in boiling dichlorobenzene 5-arylpyridazin-3(2*H*)-ones (89JHC169).

Two pathways for the preparation of 1,4-dihydropyridazine derivatives were envisaged. According to the first, dimethyl 3-oxopentane-1,5-dioate (dimethyl acetone-1,3-dicarboxylate) (**1**) was treated in ethanol and sodium acetate at 0 °C with acidic aqueous diazonium salts, prepared from aromatic or heteroaromatic amines, to give hydrazones **69** in 35–94% yields. They were next treated with DMFDMA in dichloromethane at room temperature to form the (dimethylamino) methylidene derivatives **70** as intermediates, which immediately cyclized into dimethyl 1-(hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates **71** in 72–94% yields, except for **71** (R=1*H*-1,2,4-triazol-3-yl), which was obtained in 35% yield (08ZN(63b)407) (Scheme 23).

According to the second method, **1** was treated with DMFDMA in dichloromethane at room temperature to give dimethyl 2-[(dimethylamino)methylidene]-3-oxopentane-1,5-dioate (**2**) in 78% yield after



Scheme 23

purification by column chromatography. Salts were added dropwise to an ice-cold solution in a 1:1 mixture of ethanol and water with sodium acetate aqueous (hetero)aryldiazonium to form intermediates **70**, which cyclized directly into the products **71** in 35–42% yields. They were identical to the products obtained by the first method (08ZN(63b)407) (Scheme 23).

2.10 Synthesis of heteroaryl substituted pyrimidine derivatives

2.10.1 Synthesis and transformations of 3-methyl 2-(6-hydroxy-2-phenylpyrimidin-4-yl)acetate. Simple preparation of heteroaryl substituted pyrimidines (07HCA1737)

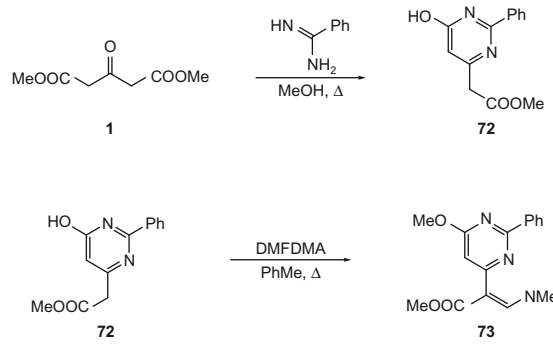
We next report a simple synthesis of pyrimidinylacetic acids and their transformations into heteroaryl-substituted pyrimidines.

There are many methods for the preparation of pyrimidines (84CHEC(3)57, 96CHEC-II(6)93). The synthesis of many aryl- and heteroarylpyrimidines involves cyclization of acyclic precursors (97S696). Palladium-catalysed reactions are useful for the synthesis of heterocycles, especially for the formation of a C–C bond to aryl and heteroaryl rings (00B1, 04CR2285, 98B1, 06CR4644). Most palladium-catalysed couplings described for carbocyclic systems employ organic bromides, iodides and triflates as substrates. Unfortunately, chlorides are unreactive (02AGE4196). In some instances, halopyrimidines (95CR2457) and 5-pyrimidinylboronic acid derivatives (90JHC2165) have been used in palladium-catalysed Suzuki–Miyaura cross-couplings (04OBC852).

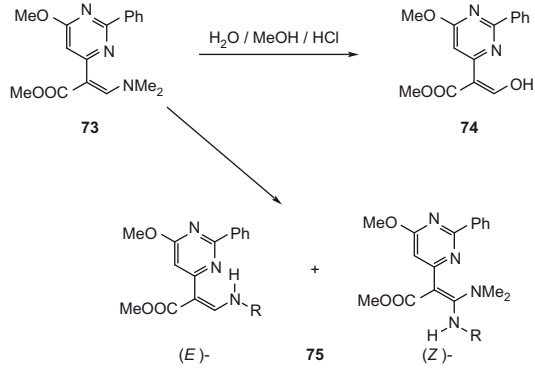
Dimethyl acetone-1,3-dicarboxylate (**1**) reacts with benzamidine to form methyl 2-(6-hydroxy-2-phenylpyrimidin-4-yl)acetate (**72**). With DMFDMA in refluxing toluene the reactive methylene group of **72** was transformed into an *N*,*N*-dimethylaminomethylidene derivative. While methylation of the hydroxyl group was taking place to give methyl (*E*)-3-(dimethylamino)-2-(6-methoxy-2-phenylpyrimidin-4-yl)propenoate (**73**) (Scheme 24).

With aqueous methanol in the presence of hydrochloric acid, hydrolysis of **73** took place to give enol **74**, while with *N*-nucleophiles such as methyl glycinate, aniline, 4-methylaniline and 4-nitoaniline in methanol containing hydrochloric acid at room temperature, substitution products **75** were formed in relatively good yields (Scheme 25).

Pyrimidines **75** exist in solution as mixtures of (*E*)- and (*Z*)-isomers; in all cases the (*E*)-isomer predominates. The conformation of the (*E*)-isomer of **7a** (R=CH_2COOMe) was determined from the heterocoupling constant between the methylidene proton and the C-atom of the ester, $^3J_{C-H}$=4.5 Hz, while ^{1}H-NMR spectra show the antiperiplanar orientation of protons in the NHCH structural element in both (*E*)-isomers (J_{NHCH}=12.6–13.4 Hz) and (*Z*)-isomers (J_{NHCH}=13.0–14.5 Hz).



Scheme 24

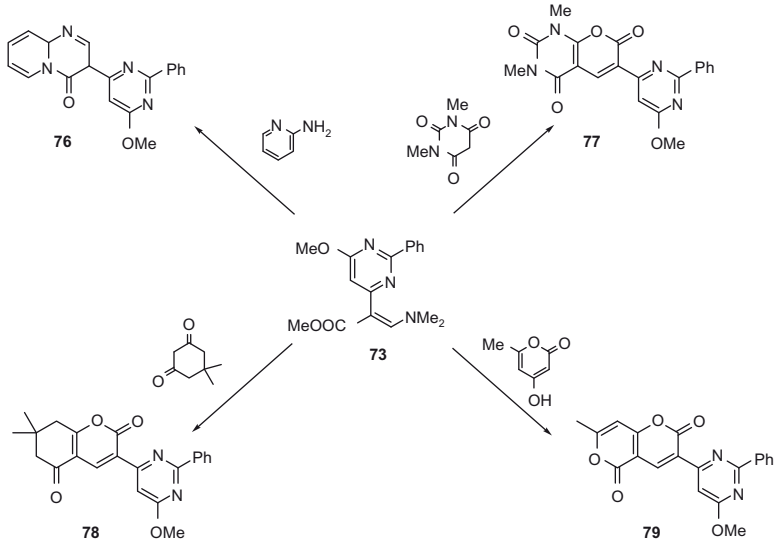


Scheme 25

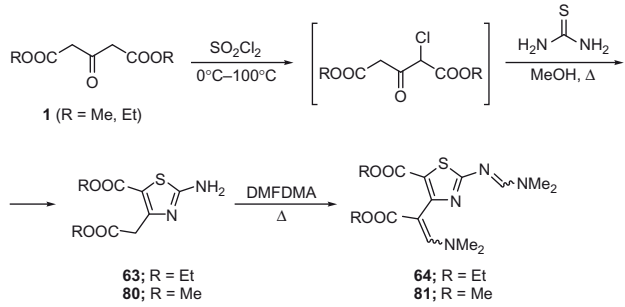
Pyrimidines **73** with dinucleophiles, such as 2-aminopyridine, 1,3-dimethylbarbituric acid, 5,5-dimethylcyclohexa-1,3-dione and 4-hydroxy-6-methyl-pyran-2(1*H*)-one, were carried out in boiling acetic acid formed 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**76**), 1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7(3*H*)-trione (**77**), 6*H*-chromene-2,5-dione (**78**) and pyrano[4,5-*b*]pyran-2,5-dione (**79**) in 30%, 67%, 56% and 73% yields, respectively (Scheme 26).

2.11 Synthesis of (pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates (09ARKIVOC(vi)137)

Pyridopyrimidines (02SOS(16)1155, 96CHEC-II(6)93, 96CHEC-II(7)561) have recently been prepared from 4-amino-6-chloro-5-phenyl-2-methylthiopyrimidine (05CHC268) and from 4-amino-1-benzyl-1,2,5,



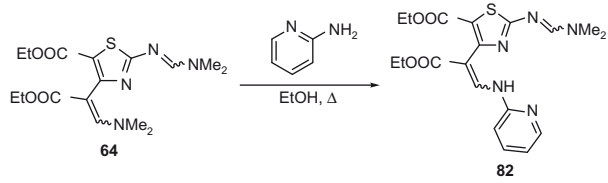
Scheme 26



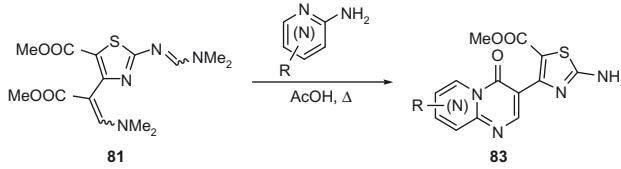
Scheme 27

6-tetrahydropyridine-3-carboxylate (01H115). They are well-known pharmacophores (03BMC59, 01JMC2133), PDE inhibitors (06EJOC4257), and inhibitors of tyrosine kinase activity at the epidermal growth factor receptor (95JMC3780).

Methyl 2-amino-4-(2-methoxy-2-oxoethyl)thiazole-5-carboxylate (**80**), prepared from dimethyl acetone-1,3-dicarboxylate (**1**), sulphuryl chloride and thiourea (46JA266), was transformed with DMFDMA into methyl 4-[1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl]-2-[(dimethylamino) methyleneamino]thiazole-5-carboxylate (**81**) in 96% yield (Scheme 27). Thiazole **64** was treated with 2-aminopyridine in hot ethanol to yield



Scheme 28



Scheme 29

intermediate **82**, which exists in two isomeric forms in a 3:1 ratio, due to the orientation around the exocyclic double bond. No attempts were made to determine their configurations (Scheme 28). Heating **81** with α-aminoheterocycles (or the corresponding dimethylamino substitution intermediates) in acetic acid under reflux gives substituted (4*H*-pyrido [1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates **83** (09ARKIVOC(vi)137) (Scheme 29, Table 2).

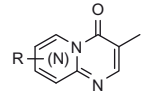
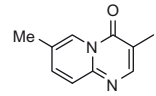
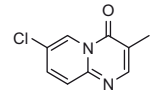
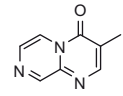
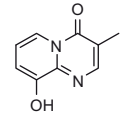
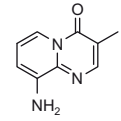
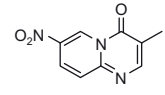
2.12 Parallel solution-phase synthesis of 1,4-dihydropyridine derivatives

We have reported syntheses of 1-substituted 1,4-dihydropyridines and their fused analogues by treatment of primary amines with *bis*-enaminones, derived from alkyl acetone-1,3-dicarboxylates (00H2033), and ethyl 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetates (07H657, 06T8126, 05TA2187, 04H609, 02H791).

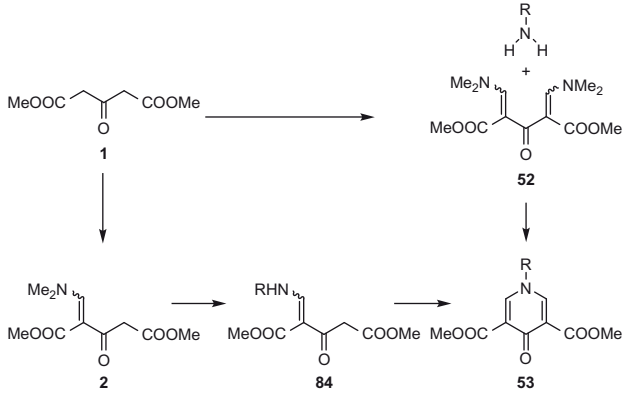
Recently we became interested in the combinatorial application of the above method, that is the utilization of the *bis*-enaminone approach in the parallel solution-phase synthesis of the title compounds (09JCC500).

Bis-enaminones **52** with primary (hetero)arylamines were employed in a parallel solution-phase synthesis of a library of 22 1,4-dihydropyridine derivatives **53**, while mono-enaminone **2** with amines produced substitution products **84**. Two methods for **53** were developed: (a) a one-step synthesis of DHPs **53** from *bis*-enaminones **52** (Method A) and (b) a two-step synthesis of DHPs **53** from the mono-enaminone **2** (Method B).

Table 2 (Pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates

Compound		Yield (%)	Time (h)
83a		36	4
83b		47	1
83c		28	1
83d		23	1
83e		52	4
83f		23	4

Generally, Method A is better and more convenient, since it affords **53** in fair yields and in >80% average purity. In terms of purity, Method B is more suited; within a library of 12 dihydropyridines **53**, 11 were analytically pure (Scheme 30).



R = 4-Me-C_6H_4, 5-Me-C_6H_4, 4-NO_2-C_6H_4, 4-F-C_6H_4, 2-I-C_6H_4, 4-HO-C_6H_4, pyridin-2-yl, 4-Me-pyridin-2-yl, 5-Me-pyridin-2-yl, 3-HO-pyridin-2-yl, 5-Cl-pyridin-2-yl, pyrazin-2-yl

Scheme 30

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CHAPTER 6

Organometallic Chemistry of Heterocycles: New Remarkable Facts

Alexander P. Sadimenko

Contents

1. INTRODUCTION

During the past decade we have been extensively reviewing the organometallic chemistry of heteroaromatic ligands. This included comprehensive reviews on organometallic compounds of furan, thiophene and their benzannulated analogues (01AHC(78)1); pyrrole, indole, carbazole, phospholes, siloles, and boroles (01AHC(79)115); pyrazole (01AHC(80)157); pyrazol-1-yl borates and related ligands (01AHC(81)167); other polyheteroatom azoles (02AHC117); chalcogenoazoles and

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their benzannulated derivatives (03AHC(84)192); boron, silicon, and phosphorus analogues of azoles (03AHC(85)1); pyridines and benzannulated pyridines (04AHC293); the η^2(N,C)-coordinated derivatives of pyridine (05AHC(88)112); B-, (Si-,Ge-) analogues of pyridine (05AHC(89)126); polypyridine ligands (07AHC(93)179, 07AHC(94)109, 08AHC(95)221, 09AHC(97)45); N,O(S)-chelating pyridines (09AHC(98)225); and aminopyridines (09AHC(99)). Moreover, a separate chapter was devoted to organometallic compounds of the five-membered heterocycles containing aluminum or a transition metal heteroatom (08MI1). Chapters on organometallic complexes of phosphinopyridines, pyridine-containing Schiff bases and mixed heterocycles, azines (six-membered heterocycles with two or more heteroatoms including nitrogen), and five- and six-membered heterocycles containing a transition metal are planned for the near future.

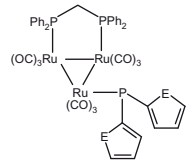
Organometallic complexes of heterocycles is a rapidly growing field; thorough, hard, and fruitful work is in progress. Especially during recent years some remarkable publications have appeared in this field, which might predetermine future new developments, related to new applications in synthetic chemistry, catalysis, and various aspects of materials chemistry, and nanotechnological applications in particular. We attempted in the current chapter to highlight some of these facts and assess their possible implications.

2. REMARKABLE ORGANOMETALLIC COMPOUNDS

2.1 Five-membered monoheterocycles

Thiophene and especially furan are quite sensitive and not easy to handle. They are prone to ring opening and ring expansion. This circumstance is widely applied in practical chemistry, especially in the problem of desulfurization of thiophene-containing fuels. Recently there appeared an original approach to study these heterocycles in the composition of furyne and thiophyne ruthenium clusters starting from their phosphine derivatives, namely, tri-2-furyl- and tri-2-thienylphosphine. They start to react with [$Ru_3(CO)_9(\mu$-dppm)] in a normal expected fashion to yield the P-coordinated **1** (E = O, S) (08JCS(D)6219). However, further decarbonylation changes the situation drastically. Phosphorus–carbon and carbon–hydrogen bonds cleave, which results in furyne and thiophyne **2** (E = O, S). Even in these circumstances thiophene still reveals its trend to ring opening. Furan appears more stable, and under thermolysis remains intact. Meanwhile, another phosphorus–carbon bond splits and phosphinidene cluster **3**

forms. Both heterocycles though cannot withstand the action of hydrogen bromide, which oxidatively adds followed by the loss of two carbon monoxide molecules. They lose their symmetric binding mode and transform into a terminal carbene **4**. Tri-2-thienylphosphine in the process of coordination with rhenium and manganese carbonyls cleaves the carbon–phosphorus bond to yield a variety of products with various coordination modes of thiophene (09OM1514), for example **5** and **6**.



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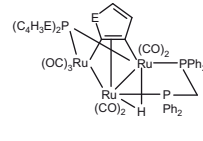

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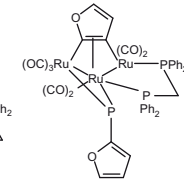

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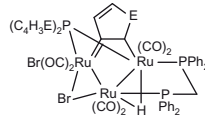

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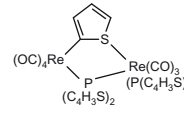

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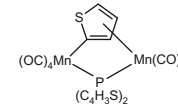

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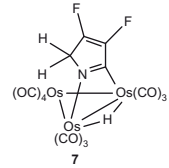
3,4-Difluoropyrrole behaves as the parent in cluster formation with $[Os_3(CO)_{10}(AN)_2]$. It undergoes familiar tautomerization and dearomatization and is N,C-coordinated in cluster **7** (09ICA291). However, decarbonylation leads to a remarkable event. A strong carbon–fluorine bond splits and rearrangement of the coordination unit to μ-η^2,η^1,η^1, **8**, takes place, and a number of such events described as C—F activation is extremely low. Another product that is familiar is **9**. It is N, C-coordinated as **7**, but one of the donor sites is a *spiro*-carbon and aromaticity is thus partially restored. The derivative of pyrrole, 3-(triphenylphosphine)-*N*-(2,6-di-i-propylphenyl)pyrrole, gives rise to a new series of N-heterocyclic carbenes, whose adducts, exemplified by **10** (R=2,6-di-*i*-propylphenyl) combine features of a carbene and phosphine, attractive for homogeneous catalysis by the products of transmetalation (08IC3949).



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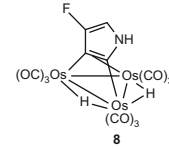

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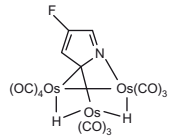

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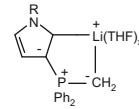

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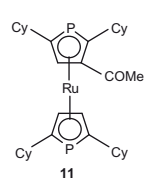
Phosphametallocene chemistry has been marked by discovery of a new reactivity mode. Apart from the well-established Friedel–Crafts acylation or Vilsmeyer formylation of these aromatic materials, they appear to form unique μ-vinylidenes. Thus, acetylation of diphospharuthenacene forms classical acetylated species **11** along with the vinylidene **12**, forming a bridge between ruthenium and phosphorus sites as a result of the C═O activation and α-hydrogen elimination (07OM6698). This reaction type seems general for different ruthenocenes and acetylating agents. Another trend is the application of phosphaferrocene as a building block for new ligands in a fashion similar to that for the parent ferrocene. Combination of phosphaferrocene and N-heterocyclic carbenes, for example **13** and **14**, is of special interest, since P-ligands with imidazol-2-ylidenes together promise high catalytic potential (08CEJ2719).



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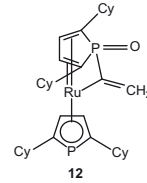

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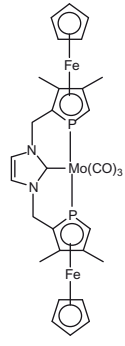

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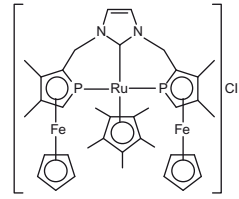

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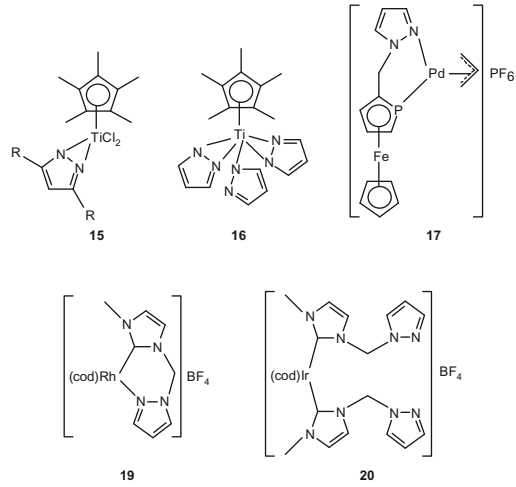
2.2 Azoles

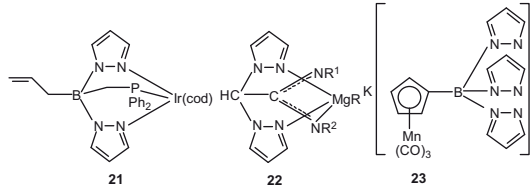
Remarkable pyrazolate products are observed in titanium pentamethylcyclopentadienyl chemistry – **15** (R = H, Me, *i*-Pr) with η^2(N,N)-coordination and **16** with a mixed mode including η^2(N,N) and η^1(N) (09IC5011). A new and useful trend exists in the organometallic

chemistry of pyrazoles, pyrazol-1-yl borate and related compounds – creation of their derivatives, where substituents carry an alternative donor function. Of interest in this respect is combining pyrazole and phosphaferrocene as illustrated by catalytic system **17** (09OM3049). Combination of imidazol-2-ylidene and pyrazole moieties revealed a sharp contrast to the rhodium **19** and iridium **20** species (06JCS(D)3927).



In the pyrazol-1-yl borate chemistry, the modern trend is creation of the ligands combining the traditional features with additional coordination units, for example phosphine in **21** (08CEJ1897). Another combination refers to pyrazol-1-yl methane with an amidinate moiety, **22** (R=C_3H_5, *t*-Bu, CH_2SiMe_3; R^1=Et, R^2=*t*-Bu; R^1=R^2=*i*-Pr) (07OM6403). Hybrid ligands based on pyrazol-1-yl borates may involve cyclopentadienyl as in the N-noncoordinated **23**, which under UV-irradiation can be transformed to partially N-coordinated **24** (07OM4663). Cymantrene gives rise to 1,3-cymantrenediyl-bridged pyrazol-1-yl borate **25**, which under UV-irradiation transforms to **26**, containing intramolecularly coordinated pyrazol-1-yl unit (09OM3079). An example of hybrid pyrazol-1-ylmethane and cyclopentadienyl ligand can be found in the organoscandium and yttrium chemistry of **27** (M=Sc, Y) and others similar to them (08IC4996) as well as titanium and zirconium complexes with alkoxide and imido ligands, for example **28** (09ICA2909). The tripodal N,N,O-ligands may be based on a *bis*(pyrazol-1-yl)borate moiety with the carboxyl-group attached to the junction of the two heterorings as in manganese(I) and rhenium(I) **29** (M=Mn, Re) (09JOM2319). Another representative of the functionalized poly(pyrazol-1-yl)methane ligands is *bis*(pyrazol-1-yl)acetic acid, which coordinates ruthenium in an η^2(N,N)-fashion, **30**, and rearranges

to η^3(N,N,O) **31** (09IC6096). An advancement in the chemistry of polypyrazol-1-yl chelating ligands are the emerging polypyrazol-1-yl aluminates exemplified by **32** (07OM6844). Development of polyheterocyclic borate chemistry leads to the unprecedented bidentate, anionic *bis*(3-*tert*-butylimidazol-2-ylidene)borates (R = Ph, Me), for which monomeric chelate **33** and nonchelating dimer **34** can be isolated (09OM3532).



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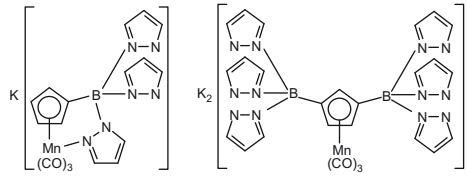

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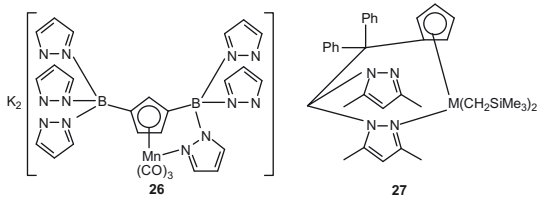

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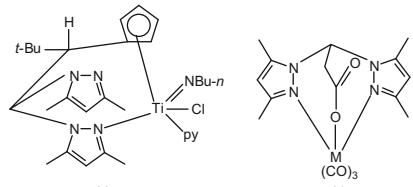

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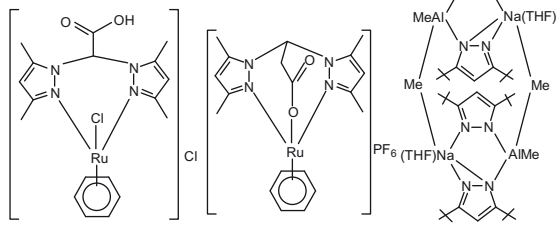
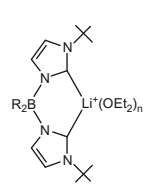


30 **31** **32**



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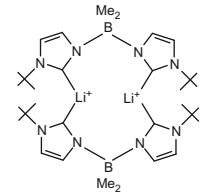

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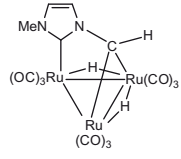
Imidazol-2-ylidene carbene organometallic chemistry is rapidly growing and the number of catalytically active compounds sharply increases every year. A relatively new trend is activation of various bonds and of the same bond in different environments. Thus, cluster **35** is characterized by C—H activation of two C—H bonds of one of the methyl substituents of 1,3-dimethylimidazol-2-ylidene (09OM1243). The first tetranuclear osmium cluster of 1,3-dimesitylimidazol-2-ylidene **36** contains the normally coordinated carbene ligand (07OM6059). Anomalies start on thermolysis in benzene: complete dehydrogenation of one of the *o*-methyl groups of a mesityl substituent, loss of two hydrogen atoms in the incoming benzene molecule, insertion of dehydrogenated benzene by way of coupling of two hydrogen-deficient moieties leading to **37**. An interesting case of intramolecular C—H activation of one of the ethyl groups occurs when half-sandwich **38** is treated with sodium *iso*-propylate to yield carbene-based iridacycle **39** (07OM4618). The problem of intramolecular C−X (X=H, Me, F, OH, NH_2, OMe, CF_3) bond activation is illustrated by transformation of N-heterocyclic carbene **40** to cyclometalated **41**, which is thermodynamically favorable due to the formation of stronger Ru—X bonds, and has been studied in depth (08OM938). Cases of intramolecular aliphatic and aromatic C—H activations are observed for series **42** (R=H, Me) (06OM4002), where R=Me, the aliphatic activation product is **43**, and for R=H, the aromatic activation product is **44**. Base-induced intramolecular C—H activation in **45** to yield **46** is another illustration (09JA4604). Studies of the cyclization reactions affording 1,2,3-triazole complexes sometimes afford exotic products similar to dinuclear **47** with a remarkable coordination mode of the bridging heteroaromatic ligands (09OM2897).



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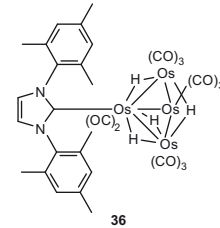

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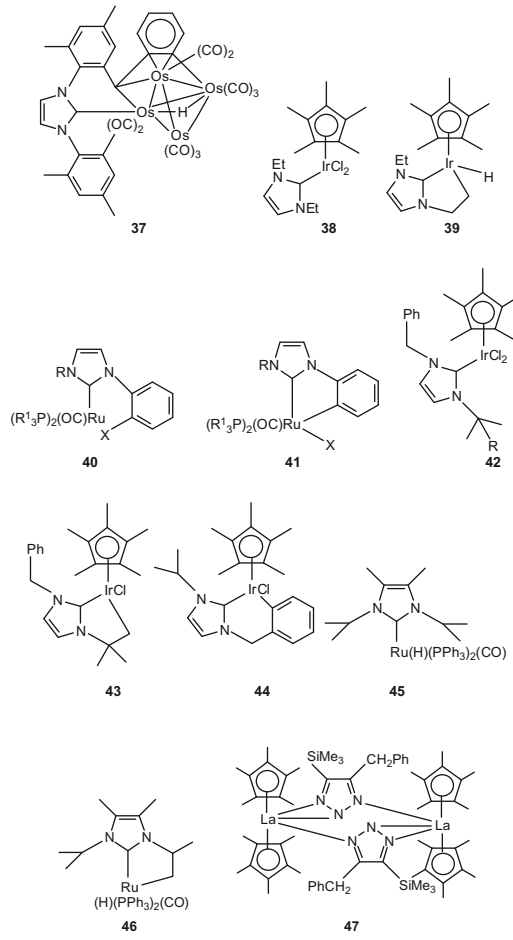
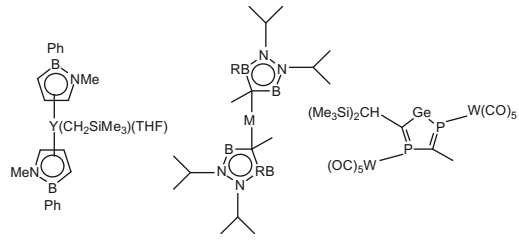
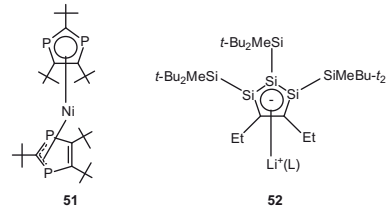


Bis(1,2-azaborolyl)yttrium alkyl **48** is the first example of a sandwich of this ligand (08OM2892). Remarkably, zinc, cadmium, and mercury sandwiches of 1,2-diaza-3,5-diborolidines **49** (M=Zn, Cd, R=Me, Ph; M=Hg, R=Me) are characterized by η^1 coordination modes (07OM3516). New analogues of azoles include the Ge,P,P-heterocycles capable of formation of η^1(P) tungsten, for example **50** (08IC1273). Diphospholes are generally characterized by η^1(P) or η^5 modes. However, nickel sandwich **51** is featured by the mixed η^3:η^5 mode, while palladium and platinum analogues are unsaturated and involve only η^3-coordination (09JCS(D) 1164). The lithium salts of 1,2,3-trisilacyclopentadienide **52** (L=THF, O=CBu-t_2) contain a new 6π-electron heteroaromatic ligand (09JA6352).

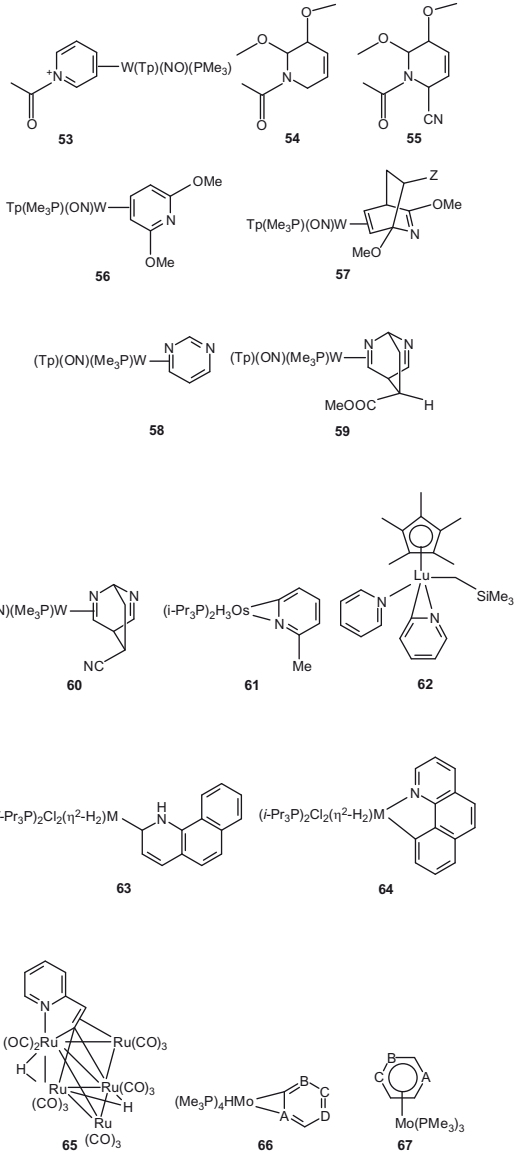




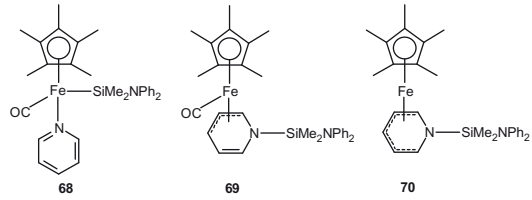
2.3 Pyridines

Much progress has been reached in the derivatization of pre-η^2-coordinated heterocycles leading to the remarkably substituted dearomatized compounds. Thus, the η^2-*N*-acylpyridinium **53** can be stereoselectively 5,6-dialkoxylated to yield **54** after decomplexation, but coordinated **54** further enters into nucleophilic addition of the cyanide ion at the C2 position of the pyridine ring, which after decomplexation results in tetrahydropyridine **55** (09OM387). Another interesting transformation is that of the η^2-2,6-dimethoxypyridine **56,** revealing the reactivity pattern of an electron-rich 2-azaallene toward various dienophiles (08OM4513). In their respective Diels-Alder cycloaddition reactions, dearomatization is accompanied by the formation of azabicyclo[2.2.2]octadienes **57**. An η^2-bound pyrimidine **58** is also a diene for Diels−Alder cycloadditions yielding such notable products as **59** and **60** (06OM5852). In this sense, activation of the NCH-endocyclic framework of 2-methylpyridine in the formation of the η^2(C,N)-pyridyl derivative **61** (08OM6188), or very rarely **62** (07OM2777), deserves attention. Benzo[*h*] quinoline in similar circumstances behaves differently (07OM5239). Initially, a 1,2-hydrogen shift from the C2-carbon to nitrogen occurs and the newly discovered N-heterocyclic carbene ligand appears in products **63** (M=Ru, Os). Under triethylamine, however, unique products are readily deprotonated and transformed to routine cyclometalated **64** (M=Ru, Os). The recently discovered phenomenon of ═C—H bond

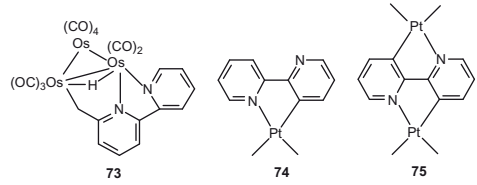
activation refers to the ruthenium clusters of 2-vinylpyridine, for example **65** (08OM5163). The less-common coordination modes are observed in the series pyridine, pyrimidine, pyrazine, and triazine and involve η^2(C,N) **66** (A=N, B=C=D=CH; A=B=N, C=D=CH; A=C=N, B=D=CH; A=B=D=N, C=CH) and η^6 **67** with the same labeling except for triazine, when thermolysis allows $\eta^2 \rightarrow \eta^6$ transformation (08ICA3221).



Another interesting development in the organometallic chemistry of pyridines is the possibility of insertion of a pyridine into the iron–silicon bond of **68** under thermolysis to yield the η^3-coordinated **69** (06OM6115). The process deepens under photolysis and the result is the η^5-coordinated pyridinium **70**. Oxidative addition of 2-bromo-3-E-pyridine derivatives E (E=NMe_2, SMe, SPh) to palladium(0) gives palladium(II) with pyridinium-derived carbene ligands **71** (09EJI1871). Another noteworthy fact is the formation of pyridin-4(1H)-ylidene remote nitrogen heterocyclic carbene complexes **72** (ML_n=$Cr(CO)_5$, $Rh(CO)_2Cl$, $Au(PPh_3)^+$) starting from Fischer carbenes (09EJI1905).

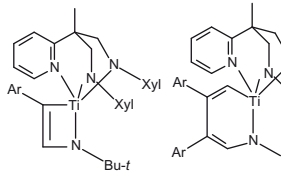


A rare case of the bridging function of 6-methyl-2,2′-bipyridine, where the 6-methyl group is cyclometalated, is **73** (08OM3018). Rollover cyclometalation **74** is among the less-common coordination modes of 2,2′-bipyridine. Moreover, the unusual dinuclear species **75** with a double C—H bond activation also exists (09OM2150). The ligand is doubly deprotonated and acts as a π-delocalized eight-electron donor.



Titanium imido complexes [Ti(NBu-*t*)(L)(py)] (L=MeC(2-C_5H_4N)(CH_2N(3,5-$C_6H_3Me_2$))$_2$) with aryl acetylenes afford [2+2] cycloaddition products **76** (Ar = Ph, *p*-Tol) (08OM2518). Reaction with a second equivalent of alkyne affords azatitanacyclohexadienes **77** (07OM5522).

A complex with Ar = Ph inserts sulfur and selenium atoms into the Ti—C bond of the azatitanacyclobutene unit to give the five-membered metallacycles [Ti(L)(η^2-N(*t*-Bu)CH = C(Ph)E)] (E=S, Se). Isonitriles insert into the Ti—C bonds to give **78** (Ar = Ph, R=Xyl, Cy, *t*-Bu; Ar = *p*-Tol, R= *t*-Bu). The reactivity pattern of 2-pyridinetetramethyldisilazane with respect to [Ru(H)$_2$(η^2-H$_2$)$_2$(PCy$_3$)$_2$] and [(η^6-COT)Ru(η^4-cod)] is extraordinary (09JA7633). It can be described as a competition between η^1(N)-coordination and Si—H bond activation. As a result, in the first case the unique η^1(N):η^2(Si, H)-coordination situation **79** arises. In the second case, the hydridotrisilyl species **80** results. η^1-Allyl platinum and palladium cationic complexes of 2,6-*bis*-diphenylphosphinomethyl-pyridine **81** react with dicationic platinum and palladium $\eta^2(\pi)$-allyls of the same ligand **82** to produce dinuclear **83** where the π-coordinated metal becomes σ-bonded and vice versa (08OM6360). The reaction involves attack of the terminal (γ) carbon atom of **81** on the coordinated olefin of **82**. Both chemical transformation schemes above reveal that chelating pyridine ligands are promising in catalysis. Another illustration is given by chelates based on 2-iminopyridine *N*-oxides **84** active in ethylene polymerization (08OM4711). Variation of Z from OMe to NO_2 govern the catalytic activity and molar mass of a polymer. Study of the polymerization catalysts leads to the discovery of a new coordination mode in a series of Schiff bases, illustrated by sandwich **85**, where one of the components is the azomethine bound *via* the heteroring in an η^5-fashion (07OM3201).



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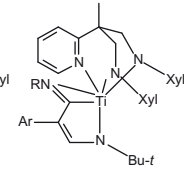

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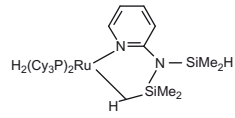

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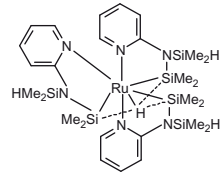

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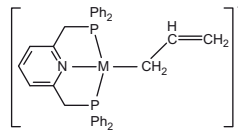

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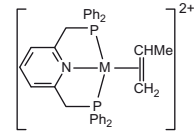

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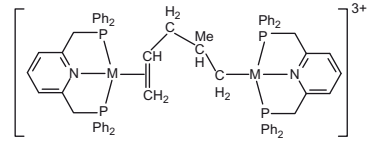

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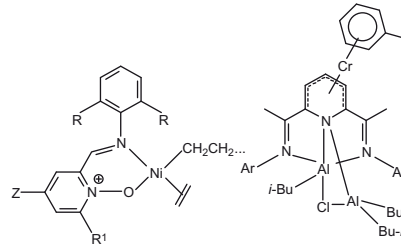

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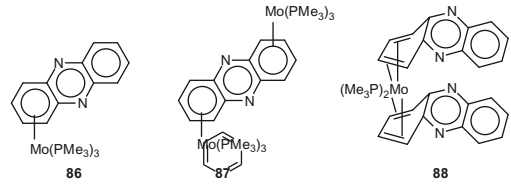
2.4 Six-membered heterocycles with two or more heteroatoms

Phenazine reveals unusual coordination modes – $\eta^6(\pi)$ **86**, μ-$\eta^6(\pi)$:$\eta^6(\pi)$ **87**, and $\eta^4(\pi)$ **88** with respect to the $Mo(PMe_3)_3$ or $Mo(PMe_3)_2$ moieties, where nitrogen atoms are not involved in the complex-formation process (09JA7828). A rare phenomenon of haptotropic isomerization is observed in the tricarbonylchromium 1,2-dihydro-2-phenyl-1,2-benzazaborine when the benzo η^6-coordionated **89,** after interaction with $KN(SiMe_3)_2$, yields potassium salt **90** and on subsequent heating is transformed to the anionic η^6-coordinated heterocyclic ring **91** (09OM506). Another case of haptotropic isomerism includes (3a,7a-azaborindenyl)tricarbonylchromium anion, when a mutual transformation between **92** and **93** is observed (06OM3463). Pentamethyl-2,3-dihydro-1,3-diborole unexpectedly forms dinuclear triple-decker **94**, which includes the bridging μ,η^6:η^6-hexahydro-tetraboranaphthalene (09JOM1718). 2-Vinyl-1,2-azaboratabenzene forms triple-decker **95** where the heteroaromatic ligand reveals a mixed bridging mode: η^6 with respect to one ruthenium moiety and η^1(Cl)-η^1(N)-η^2(C═C) to another (09JOM1036). Azine chemistry is also marked by nitrogen heterocyclic silicon carbene ligands and their adducts exemplified by **96** and **97** (09JA7232, 09JA7562), the latter containing a unique betaine-like Si═O π system.



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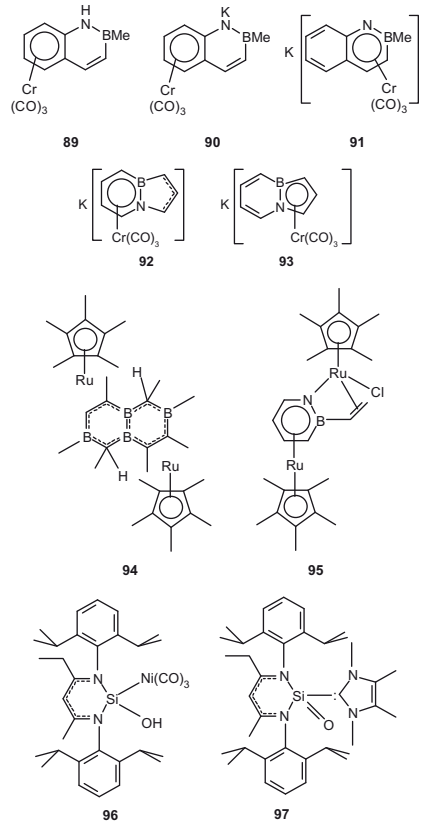
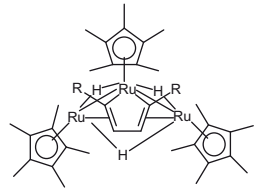


2.5 Five- and six-membered rings with transition metal heteroatoms

In the series of metallacyclopentadienes, of special interest is a series of *closo*-ruthenacyclopentadienes **98** (R=Me, Et, *n*-Pr, *n*-Bu, *n*-C_5H_{11}), in which the heterocycle is η^2-coordinated (08OM18). The ruthenacyclobutenylidene **99** is among remarkable metallacycles (09JOM1). The unique compound ruthenabenzofuran **100** under protonation using $HBF_4 \cdot OEt_2$ gives the cationic ruthenabenzene **101**, while with HCl forms the neutral ruthenabenzene **102** (09OM567). Reactions of ring expansion and ring contraction are now popular in metallacycles. Hafnacyclopropene **103** inserts ethylene, which leads to hafnacyclopentene **104** and further hafnacyclopentane **105** (09JA4463). Iridacyclopentadiene **106** readily transforms into iridabenzene **107** with methyl triflate and lithium chloride (08OM451). The reaction of **107** with $(C_5H_5NH)(Br_3)$ and lithium bromide is an aromatic electrophilic

substitution oriented to the *p*-position with respect to the SMe-substituent in **108**. Another interesting transformation is that from iridacyclobutadiene **109** to formally iridabenzothiophene **110,** including an iridabenzene aromatic ring (07OM2167). Iridacycloheptatriene **111** under oxo-transfer oxidizing reagents contracts its ring and gives iridabenzene **112** (07OM3403). A new type of triple-deckers exemplified by **113** (M=Co, Ni) is based on 9-nickelafluorenyl lithium (09IC4934). Among the new metallaheterocycles of interest are azanickelacyclopentadienes **114**, the products of oxidative cyclization of acetylene and imines in the presence of nickel(0) and azaaluminacyclopentadienes **115**, which follow from the nickel precursors by the route of double transmetalation with trimethyl aluminum (09JA9160).



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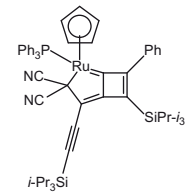

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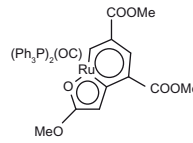

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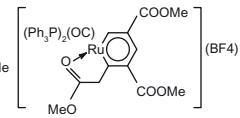

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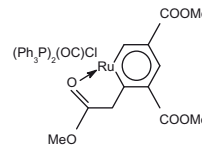

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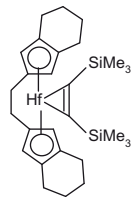

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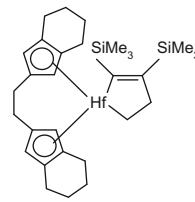

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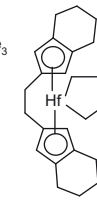

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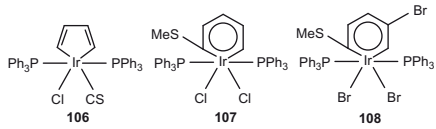

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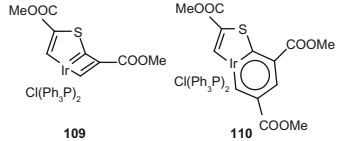

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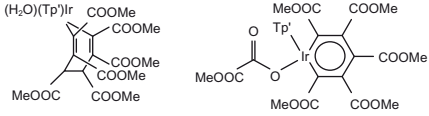

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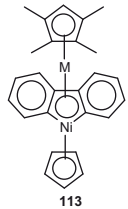

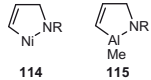

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3. CONCLUSION

1. Derivatized furan and thiophene containing phosphine moieties in cluster-formation cleave their C—P bonds but remain intact in the furyne and thiophyne clusters, which allows study of the nature and reactivity of these heterorings. Fluoropyrrole features a rare event of C—F activation, while phosphinopyrrole gives rise to a new N-heterocyclic carbene in combination with a phosphine donor. Phosphametallocene chemistry has been marked by the discovery of a new pattern of acetylation and creation of the ligands combining phosphametallocene and imidazol-2-ylidene carbene functions.
2. Azole chemistry is also characterized by a combinatorial approach when two principally different donor functions are linked in a ligand in search of new efficient catalytic systems. Another development is the creation of new ligands based on polypyrazol-1-yl aluminates and poly-imidazol-2-ylidene borates. Imidazol-2-ylidene adducts and clusters have been especially deeply studied from the viewpoint of intramolecular bond activation processes.

The range of the new ligands and their coordination modes has considerably been extended in the analogues of azoles.

3. The η^2-coordinated pyridines and some azines provide a reactivity pattern that allows the preparation of a variety of new derivatives of aromatic and dearomatized six-membered heterocycles. The profound study of the insertion and oxidative addition reactions in a series of pyridine organometallics allowed the discovery of new coordination modes and the preparation of pyridin-2-ylidene carbenes. The modes of reaction of the chelate complexes of pyridines provide new knowledge about transition metal complex catalysis.
4. New coordination situations are quite numerous in the organometallic compounds of six-membered heterocycles with two or more heteroatoms, where the fused B,N-rings reveal a rare haptotropic isomerism.
5. *Closo*-ruthenacyclopentadienes, ruthenabenzofuran, iridabenzothiophene, azanickelacyclopentadienes, and others comprise an entity of new rings containing transition metals as heteroatoms. Reactions of ring expansion and ring contraction allow the preparation of such rings with a variety of substituents.

LIST OF ABBREVIATIONS

Ar	aryl
Bu	butyl
cod	cyclooctadiene-1,5
Cy	cyclohexyl
dppm	diphenylphosphinomethane
Et	ethyl
Me	methyl
Ph	phenyl
Pr	propyl
py	pyridine
THF	tetrahydrofuran
Tol	tolyl
Tp	tris(pyrazol-1-yl)borate
Tp′	tris(3,5-dimethylpyrazol-1-yl)borate
Xyl	xylyl

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CHAPTER 7

The Chemistry of the [1,2,3] Triazolo[1,5-*a*]pyridines: An Update

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1. INTRODUCTION

[1,2,3]Triazolo[1,5-*a*]pyridine **1** is one of five heterocyclic systems that includes the general class of triazolopyridines **1–5** (Figure 1). Four reviews have been published about **1–5** (83AHC79, 96CHEC-2(7)363, 96CHEC-2(8)367, 02AHC1), and one about the [1,2,3]triazolo[1,5-*a*] pyridine **1** (02MI1).

This review covers the literature from 2001 to the beginning of 2009 on the chemistry of **1**, a small but versatile family of compounds with an interesting chemistry.

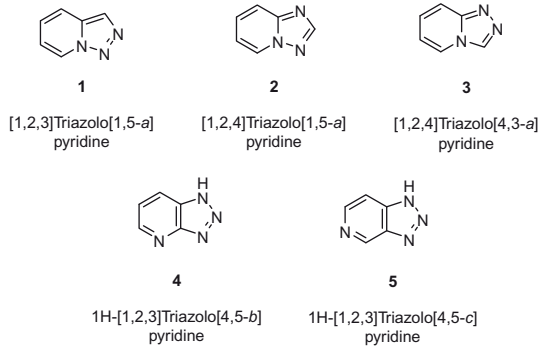


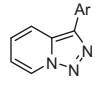
Figure 1

2. PHYSICAL PROPERTIES AND THEORETICAL CHEMISTRY

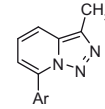
2.1 Electronic spectra

A study of fluorescence spectra of a series of 3-aryl- (series A, compounds **6**) and 3-methyl-7-aryl-[1,2,3]triazolo[1,5-*a*]pyridines (series B, compounds **7**) has been reported (06TL8101) (Figure 2). All compounds studied are highly fluorescent. The fluorescence excitation, emission maxima and quantum yields of both series are recorded in Table 1. The conjugation of triazolopyridine with an aryl or heteroaryl group gives highly fluorescent compounds. The position of substitution causes no significant change in the emission band. In both series, the presence of one halogen substituent in the 6-position of a 3-pyridyl group does not have a significant effect in the fluorescence emission band, but these halo derivatives have the greatest relative fluorescence intensity. The quantum yields have been calculated taking anthracene dissolved in CH_2Cl_2 as a reference (ϕ_{ant}=0.42). In general, the quantum yields are very high, compounds **7g** and **7h** particularly having pyridyl functions attached to the six-membered ring, displaying quantum yields almost double that of the reference.

A condensed triazolopyridine system, the compound **8b** has been examined as a chemosensor (Figure 3) (06JOC9030). It presents a very intense fluorescence emission at 464 nm (λ_{exc}=398 nm). The quantum yield Φ of **8b**, calculated using an ethanol solution of anthracene as reference, is 0.13. Interaction with Cu^{2+} produces a quenching of the fluorescence while interaction with Zn^{2+} leads to a quenching of the fluorescence and a bathochromic shift. The crystal structure of $[Zn(\mathbf{8b})(H_2O)_3](ClO_4)_2] \cdot H_2O$ complex shows the coordination of Zn^{2+} through the terpyridine moiety. The octahedral site is completed by three water molecules. Interaction of the Zn^{2+} complex with the anions sulphate, nitrate, nitrite and dihydrogenphosphate in ethanol produce hypsochromic shifts and restoration of the fluorescence whose magnitude depends on the anion involved. The maximum interaction is observed for $H_2PO_4^-$. Interaction of the Zn^{2+} complex with the amino acids L-aspartate and L-glutamate has also been explored showing a higher interaction with L-aspartate.



6 a Ar = C_6H_5
b Ar = *p*-$MeOC_6H_4$
c Ar = *p*-MeC_6H_4
d Ar = *m*-MeC_6H_4
e Ar = *o*-MeC_6H_4
f Ar = *p*-BrC_6H_4
g Ar = 3-pyridyl
h Ar = 2-pyridyl
i Ar = 6-fluor-3-pyridyl
j Ar = 6-chloro-3-pyridyl



7 a Ar = C_6H_5
b Ar = *p*-$MeOC_6H_4$
c Ar = *p*-MeC_6H_4
d Ar = *m*-MeC_6H_4
e Ar = *o*-MeC_6H_4
f Ar = *p*-BrC_6H_4
g Ar = 3-pyridyl
h Ar = 4-pyridyl
i Ar = 6-fluor-3-pyridyl
j Ar = 6-chloro-3-pyridyl

Figure 2

Table 1 Relative fluorescence intensities and quantum yields (series A and B)

Compound	λ_{max} (nm) Excitation	λ_{max} (nm) Emission	Relative fluorescence intensity (**6j**=100)	Φ
6a	360	431	9.61	0.12
6b	370	448	43.55	0.44
6c	364	440	18.53	0.29
6d	361	432	12.24	0.54
6e	348	431	7.34	0.40
6f	363	431	11.89	0.38
6g	357	424	5.64	–
6h	361	412	6.09	–
6i	364	432	93.88	–
6j	365	431	100	0.10
7a	365	436	9.35	0.13
7b	363	428	8.31	0.12
7c	372	428	13.59	0.25
7d	368	437	4.01	0.12
7e	351	430	4.40	0.08
7f	377	442	3.75	0.62
7g	374	438	1.21	0.69
7h	378	448	22.15	0.89
7i	351	439	22.64	–
7j	359	439	36.09	0.52

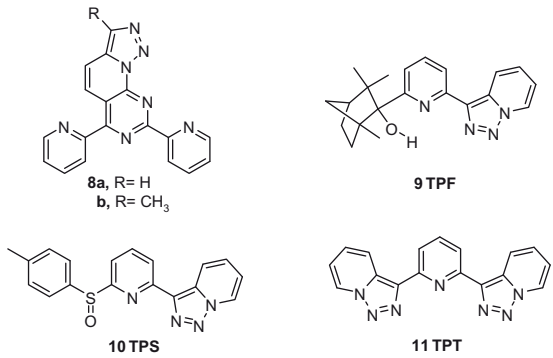


Figure 3

Three tridentate ligands, chiral alcohol **9** (**TPF**) (07T10479), sulphoxide **10** (**TPS**) (07TL6896, 08T3794) and pyridine **11** (**TPT**) (04T5785), (Figure 3), based in the triazolopyridine nucleus possessing fluorescent properties, have also been tested as chemosensors for metal ions (09NJC2102). These ligands (**9**, **10** and **11**) are highly fluorescent and soluble in organic solvents; small addition of water provided no modification of the fluorescent properties**.** The fusion of a triazole

(electron-donating group) and a pyridine (electron acceptor) provides extremely interesting fluorescence properties to these three ligands. The close spectral characteristics and quantum yield of the three compounds can be attributed to the fact that the fluorophoric behaviour is marked by the triazolopyridine–pyridine system. The fluorescence of **TPS** and **TPT** keeps constant with time, the **TPF** decreases significantly, which can be associated with the occurrence of some precipitation.

The spectroscopic characteristics of the Zn^{2+} complexes are analysed. **TPF**, **TPS** and **TPT** have been used to obtain Zn(II) complexes by reaction with zinc chloride etherate. (09NJC2102). FAB or ESI MS supports the formation of 1:1 $[Zn(\mathbf{L})]^+$–Cl aggregate in all cases. With compound Zn^{2+}-**TPT** ESI MS also show the presence of a 1:2 complex $[Zn(\mathbf{TPT})_2]Cl^+$.

The spectroscopic characteristics of the Zn^{2+} complexes are analysed in 98:2 v/v ethanol/water solution of $Zn(ClO_4)_2$ and the ligands **TPS** and **TPT**. The system Zn^{2+}-**TPF** was not analysed due to the above-mentioned precipitation.

Although addition of Zn^{2+} to **TPS** produces very slight changes in the fluorescence intensity and quantum yield values, addition of Zn^{2+} to **TPT** solutions leads to very significant chelation enhancement of fluorescence (CHEF). The intensity and quantum yield increase after addition of 1 equiv. of Zn^{2+} to **TPT** very significantly. The fluorescence increase is accompanied by a small (8 nm) hypsochromic effect. These fluorescence properties can be explained by a PCT mechanism (99MI1). The shift in the position of the band is smaller than those that are previously reported for the triazolopyridine molecule in previous work (06JOC9030). While in this work, coordination of Zn^{2+} occurs at the electron-donating pyridine fragments, in systems mention above, Zn^{2+} coordination involves both the electron-accepting pyridine fragment and the electron-donating triazolopyridine ring compensating the effect.

The less significant changes observed for **TPS** can probably be due to the high electron-withdrawing properties of the sulphoxide.

2.2 Infrared spectra

No detailed analysis of the infrared spectra has been published.

2.3 Mass spectra

There are many reports of the use of high resolution mass spectroscopy (HRMS) for analysis of the composition of the new triazolopyridines described in almost all the references cited.

2.4 Nuclear magnetic resonance spectra

All new triazolpyridines reported include data on ^{1}H-NMR and ^{13}C-NMR spectra. In some special cases correlations are reported. Detailed assignments are available for compounds **8** (Figure 3) (06JOC9030); **12–17**

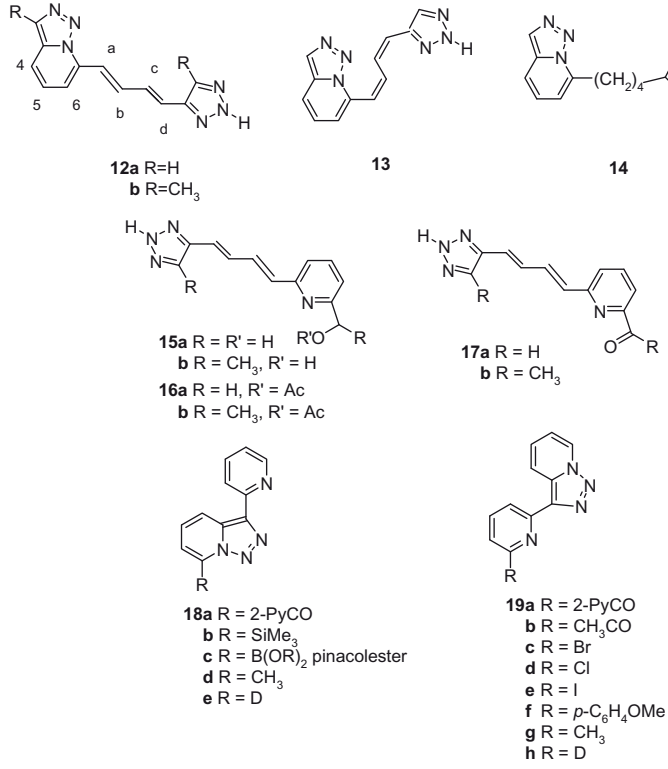
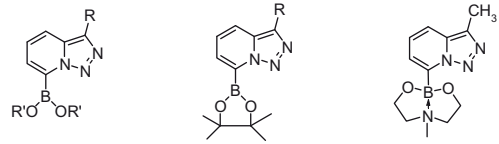


Figure 4

(Figure 4) (02ARK146); **18**, **19** (Figure 4) (05OBC3905); **20–23** (Figure 5) (04T4887) and **24**, **25** (Figure 5) (08ARK73).

2.5 Electron spin resonance spectra and cyclic voltammetry

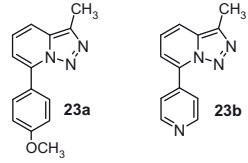
The electron spin resonance (ESR) spectra of free radicals obtained by electrolytic reduction of some triazolopyrirdyl pyridyl ketones **26** (05SAA2261), **24a–c**, **25**, **19a** and **27–31** (Figures 4–6) (08SAA703) have been measured in dimethylsulphoxide (DMSO). The hyperfine patterns indicate that the spin density delocalization is dependent on the ring present in the molecule. The electrochemistry of these compounds has been characterized using cyclic voltammetry in DMSO as solvent. When one carbonyl group is present in the molecule one step in the reduction mechanism is observed, and when two carbonyl groups are present two steps were detected. The first wave is assigned to the generation of the corresponding free radical species, and the second wave is assigned to the dianion derivatives. Stable free radicals are generated using electrochemical reductions at a potential corresponding to the first wave obtained from the voltammetric experiments.



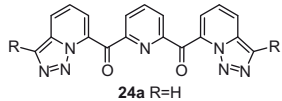
20a R=H, R'=H
b R=CH_3, R'=H
c R=2-Py, R'=h

21a R=H
b R=CH_3
c R=2-Py

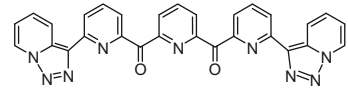
22



23a **23b** **23c** **23d**

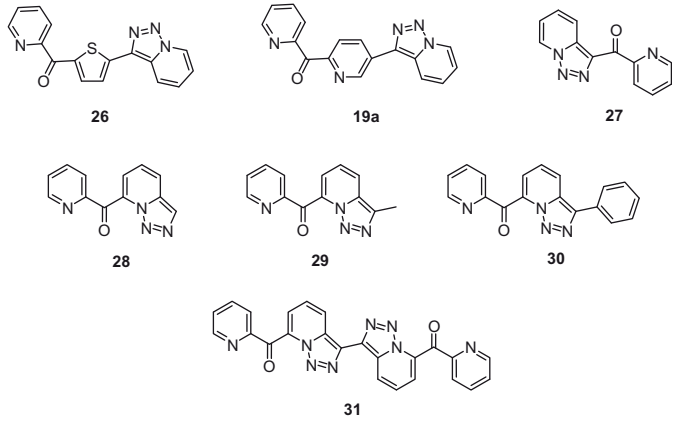


24a R=H
b R=CH_3
c R=Ph



25

Figure 5



26 **19a** **27** **28** **29** **30** **31**

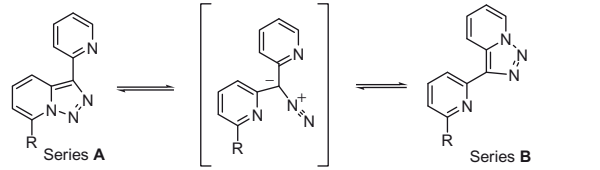
Figure 6

2.6 Theoretical chemistry

An experimental (^{1}H-NMR) and theoretical (DFT/B3LYP/6-31G*) study has been carried out of the ring-chain isomerization of the 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyrid-7-yl derivatives (**A**), that are in equilibrium with the intermediate diazo form and may undergo a new ring-chain isomerization into 6-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-2-pyridyl

derivatives (**B**) (Scheme 1) (05OBC3905). Based on the calculations, a mechanism of several steps is proposed (Figure 7). The experimental results as well as the calculations led to the conclusion that the **A**/**B** ratio depends on the electronic properties of the substituents. Electron-donating substituents favour the **A** form, electron-withdrawing substituents favour the **B** form and the case where R=Me both forms are present (75% of **A**, 25% of **B**).

A general study of the energetic profile and geometrical changes in the ring-chain isomerization process of [1,2,3]triazolo[1,5-*a*]pyridines, and



18a R = 2-PyCO
b R = $SiMe_3$
c R = $B(OR)_2$ pinacolester
d R = CH_3
e R = D
40a R = PPh_2
b R = P(*p*-$PhCH_3$)$_2$

19a R = 2-PyCO
b R = CH_3CO
c R = Br
d R = Cl
e R = I
f R = *p*-C_6H_4OMe
g R = CH_3
h R = D
41a R = PPh_2
b R = P(*p*-$PhCH_3$)$_2$
42 R = PSe(*p*-$PhCH_3$)$_2$

Scheme 1

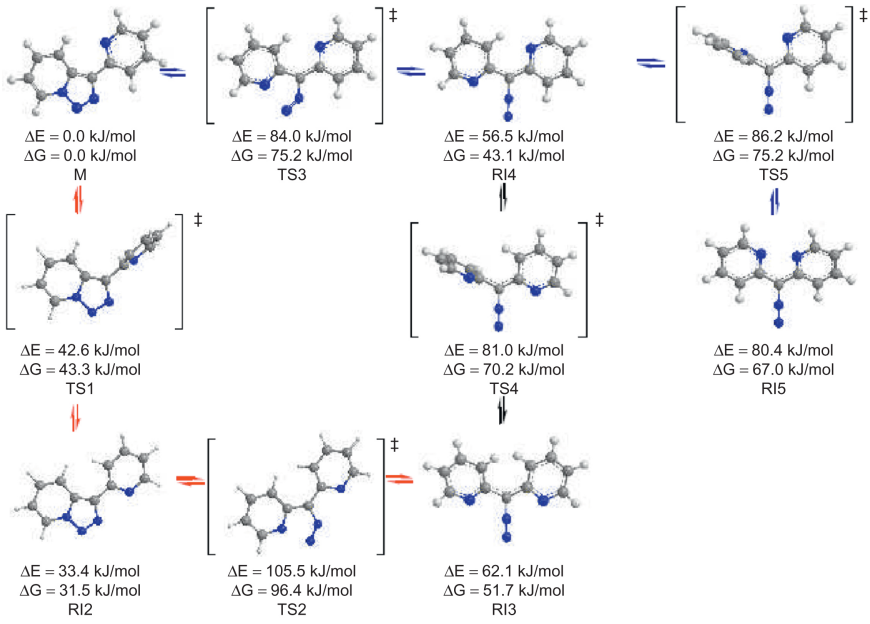


Figure 7

the effects induced by the substitution, protonation and deprotonation over the equilibrium has been undertaken by means of DFT calculations at the B3TYP/6-31+G(*d*,*p*) computational level (08T11150). In addition, the electronic characteristics of the structures obtained have been analysed by means of the atoms in molecules (AIM), electron localization function (ELF), molecular electrostatic potential (MEP) and natural bond orbital (NBO) methods. Also, a specific study of the lithiation reaction, the most widely used method of functionalization of triazolopyridines, and the possible influence of the open forms on this process was studied.

The results show the important effect of the substitution on the equilibrium as a function of the electronic properties of the functional groups, especially in the C3 and C7 sites of the triazolopyridine ring. Therefore, deprotonation produces an effect qualitatively similar to the substitution by electron-releasing groups. The position of protonation and the effect of protonation and deprotonation on the isomeric equilibrium have been discussed and some results are coherent with the experimental data described in the literature. From the results of the specific study of the regioselective reaction of lithiation it can be deduced that the process could be explained by a thermodynamic criterion due to the relative stability of the lithio derivatives.

Preliminary calculations on compound **8b** (Figure 3), show that the electron density accumulates in the triazole part that acts as an electron-donor group towards the electron-accepting part residing in the 2,4-dipyridin-2-yl-pyrimidine moiety (06JOC9030).

AM1 and DFT calculations were performed to obtain the optimized geometry of compound **26** (Figure 6). The radical structure showed a small distortion with respect to the neutral molecule. B3LYP/6-31G* calculations gave the theoretical hyperfine constants, using the geometries from AM1 calculations and the results are in agreement with the assignment of the hyperfine constants. The radical structure optimized is in agreement with the experimental hyperfine coupling. A thiophene group showed a theoretical structure in which the thiophene group is almost in the same plane as the pyridine ring (05SAA2261). The same calculations have been done for compounds **19a**, **24a–c**, **25** and **27–31** (Figures 4–6) (08SAA703). Fully optimized geometries for the electron-paired and anion radical molecules at the AM1 level have been obtained. All radical structures showed a small distortion with respect to the analogous neutral molecules. B3LYP 6-31G* calculations were performed to obtain the theoretical hyperfine constants, using the geometries from AM1 calculations. Compounds **19a**, **28**, **29** do not have the pyridine ring in the same plane as the triazolopyridine ring (about 46° between rings), however, **27** shows an angle of 89° between these rings. The theoretical hyperfine coupling in **27** shows that the spin density is located in the triazolopyridine ring at hydrogen 8, however, for **19a** and **28–31**, the theoretical hyperfine constants

show that the spin density is more delocalized in the triazolopyridine ring. With respect to **24a–c**, the spin density is localized in the central pyridine ring. Molecule **25** shows that the spin density is localized mainly in the triazolopyridine rings. However, the unpaired electrons also are delocalized in the pyridine rings.

2.7 X-ray crystallography

The structure of the condensed triazolopyridine **8b** (05ARK71) and its $[Zn(\mathbf{8b})(H_2O)_3](ClO_4)_2] \cdot H_2O$ complex **32** (06JOC9030), have been determined by X-ray diffraction analysis (Figures 8 and 9).

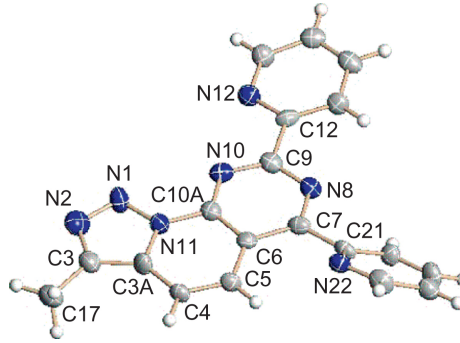


Figure 8

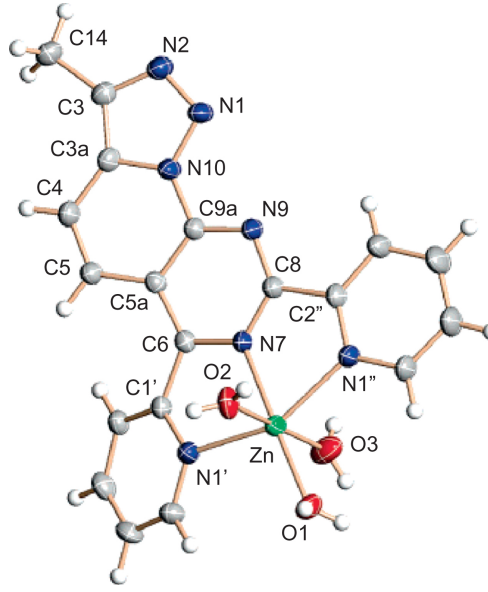


Figure 9

The molecular structure of **8b** shows a planar triazolopyridopyrimidine moiety and two pyridine rings, both rings being twisted with respect to that moiety. The pyridine ring containing C(12) is slightly bent while the pyridine ring having C(21) is strongly twisted with respect to the triazolopyridopyrimidine plane. In the crystal, molecular layers are formed through C–H···N weak hydrogen bonds. The layers self-assemble along the *b* axis showing ring stacking. The molecular assembly produces nanotubes along the *b* axis where the water molecules are included.

Compound **33** (**TP**) (Figure 10) is an interesting ligand in coordination chemistry, complexes **34** [Fe(**TP**)$_3$](BF$_4$)$_2$ (Figure 11), **35** [Fe(**TP**)$_2$(NCS)$_2$]-2CHCl$_3$ (Figure 12) (03IC4782, 09CEJ2384) and **36** [Ru(**TP**)(bpy)$_2$)Cl$_2$] (08ICC595) (Figure 13) are described and their structures determined by X-ray diffraction analysis.

Compound **37** (Figure 10) forms a *bis*(2,2′-bipyridine)ruthenium(II) complex **38** [Ru(**37**)(bpy)$_2$Cl$_2$]. An X-ray crystal structure shows that it

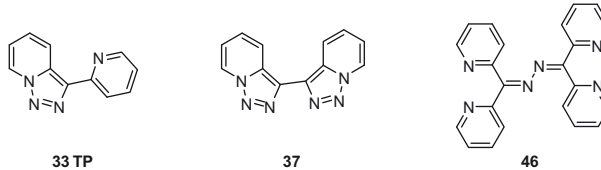
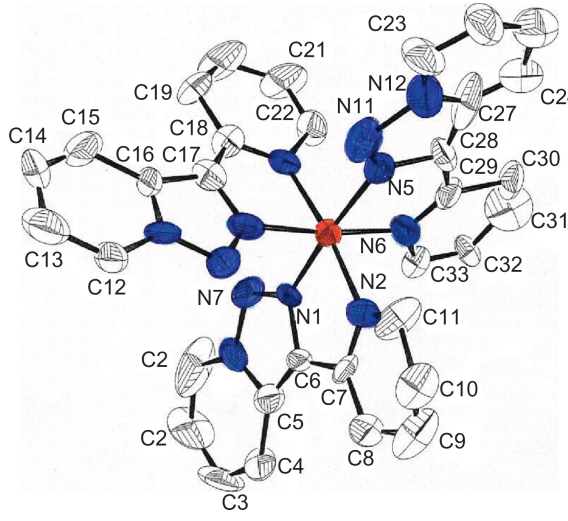
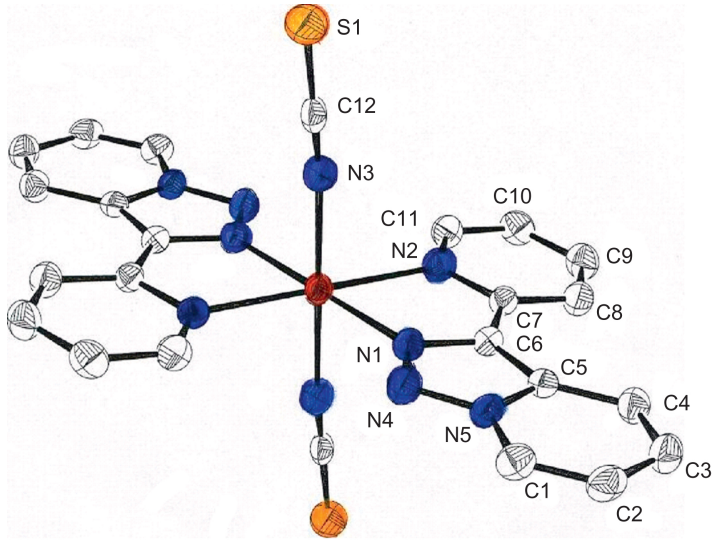


Figure 10



[Fe(**TP**)$_3$](BF$_4$)$_2$

Figure 11



$[Fe(\mathbf{TP})_2](NCS)_2 \cdot 2CHCl_3$

Figure 12

crystallizes in the triclinic space group P-1, with a full cation in the asymmetric unit, despite the option for higher symmetry associated with the C_2 symmetry of this species (Figure 13) (08ICC595).

A new tetranuclear cubane complex has been synthesized from an assembly of Cu^{II} ions and the polydentate ligand **19a** (Figure 4). The crystal structure of the tetranuclear cubane, $[Cu(\mathbf{19a^*})]_4(NO_3)_4.8H_2O$ where the ligand **19a*** is the haemiacetal of the methanone **19a**, is reported (Figure 14) (07EJI4574).

X-ray diffraction analysis of the complex **39** $[Zn(\mathbf{TPT})_2](ClO_4)_2 \cdot 1/2CH_3CN$ (where **TPT** is **11**, Figure 3) has been performed. The asymmetric unit of **39** consists of two almost equivalent $[Zn(\mathbf{TPT})_2]^{2+}$ cations, ClO_4^- counter anions and one CH_3CN molecule. The cationic complexes (Figure 15) display distorted octahedral geometry with meridional arrangement of the *bis*(triazolopyridino)pyridine moieties, which behave as tridentate ligands through the nitrogen donor atom of the central pyridine ring and the nitrogens placed at the 2-positions of the triazole rings. The bond distances of the metal ion with the pyridine nitrogens (average distance 2.13 Å) are slightly shorter than those with the triazolo nitrogens (average distance 2.20 Å). The ligand is slightly domed with a mean angle between the triazolopyridine units of *ca.* 10°. The crystal packing shows π–π-stacking interactions between the cationic units, which give rise to a sort of pillar-like chains (09NJC2102).

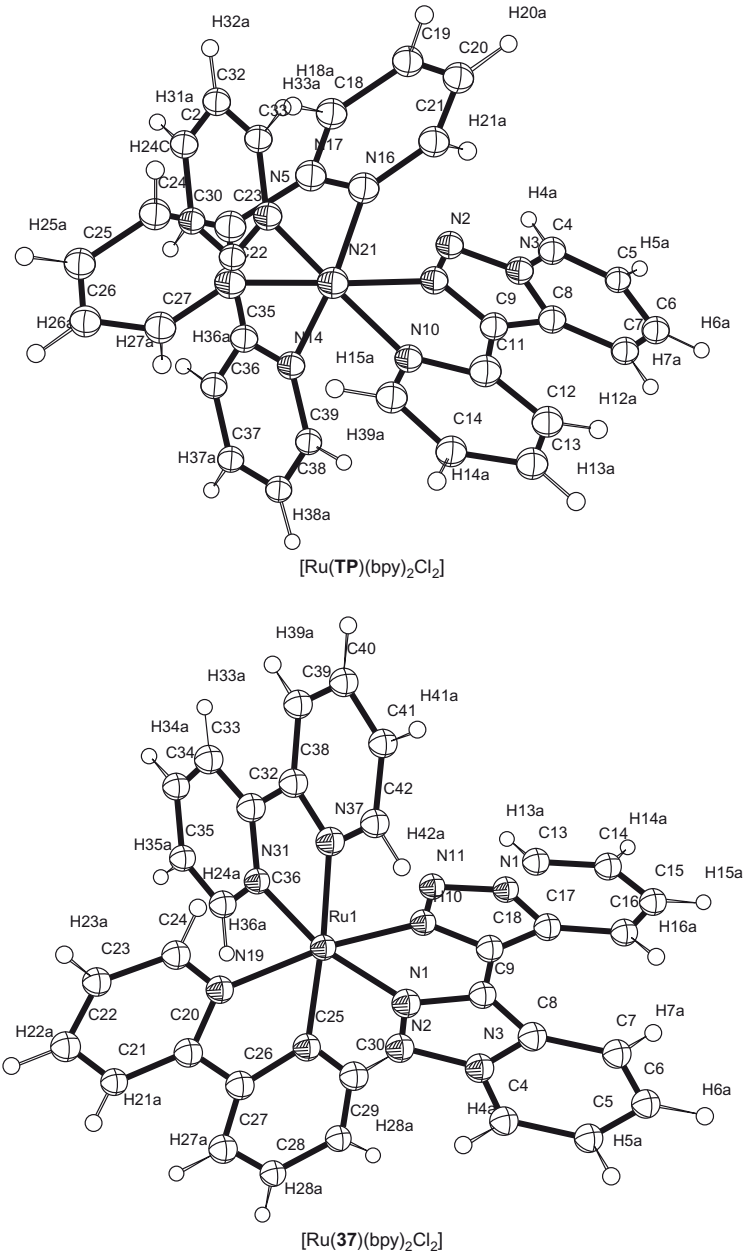
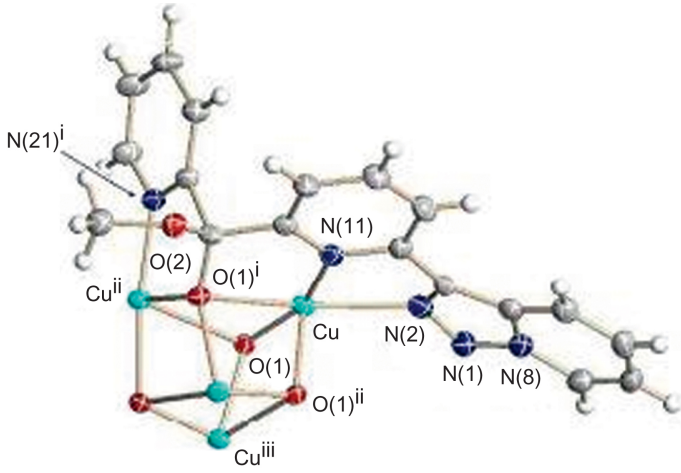
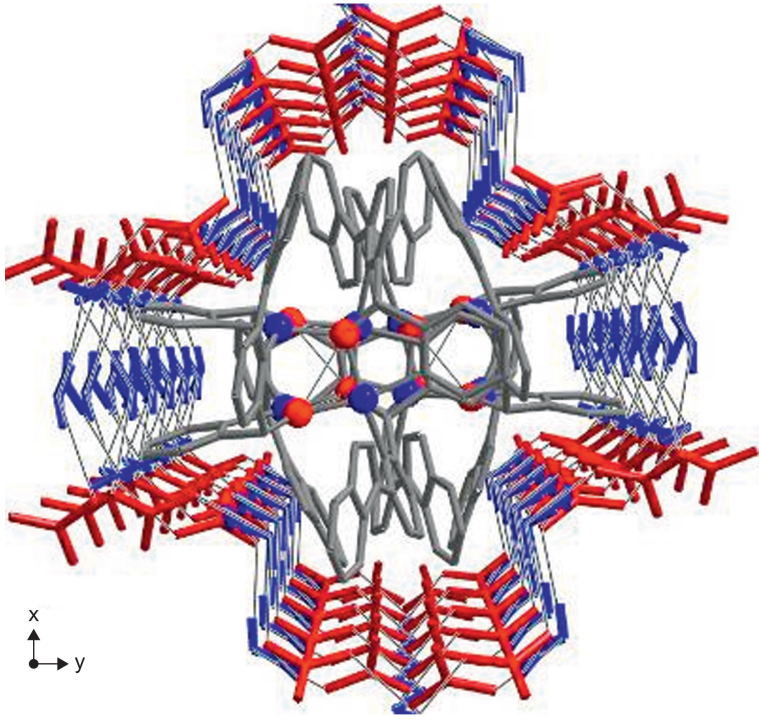


Figure 13

A single crystal from the ring-chain isomer of phosphine **41a** (Scheme 1) has been isolated and its structure confirmed by X-ray analysis (Figure 16). In solution, the pure isomer **41a** undergoes equilibration with isomer **40a**.



Representative fragment of the $[Cu(L)]_4^{+4}$



View of a dodecagonal channel with two adjacent $[Cu(L)]_4^{+4}$

Figure 14

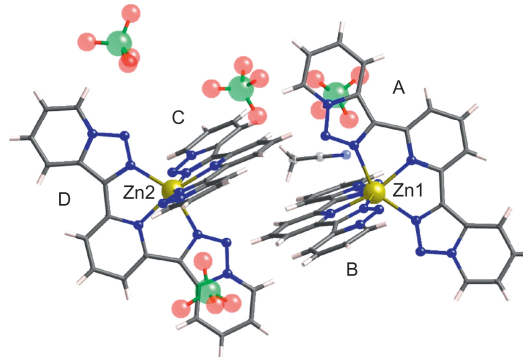
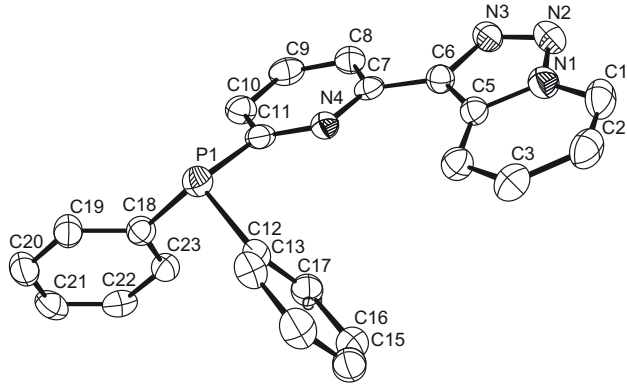
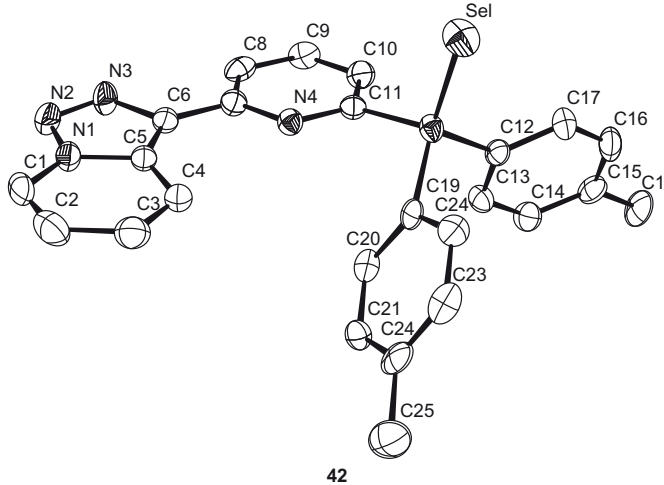


Figure 15



41a



42

Figure 16

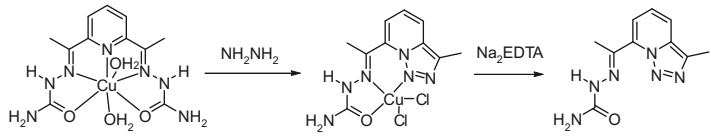
When the phosphine **40**⇌**41** are converted into their selenide **42**, the equilibrium is completely shifted towards the electron-acceptor structure **B**. The structure of this selenide could also be confirmed by single crystal X-ray analysis (Figure 16) (09DT5068).

3. SYNTHESIS OF THE [1,2,3]TRIAZOLO[1,5-*a*]PYRIDINE SYSTEM

The most commonly used synthesis of [1,2,3]triazolo[1,5-*a*]pyridines remains that from the hydrazones of 2-pyridyl-carboxaldehydes or -ketones by oxidation. Some hydrazones give triazolopyridines when boiled in methanol in the presence of air, but all other reported cases require an added oxidant. The use of the most common oxidants illustrates the versatility of the synthesis. Nickel peroxide, potassium ferrocyanide and bicarbonate, air and a copper-II salt, manganese dioxide or (diacetoxyiodo)benzene have been used (02AHC1). An alternative route from tosylhydrazones of 2-pyridyl-carboxaldehydes or ketones by treatment with base, usually morpholine, has been used for high yields of sensitive materials (02AHC1).

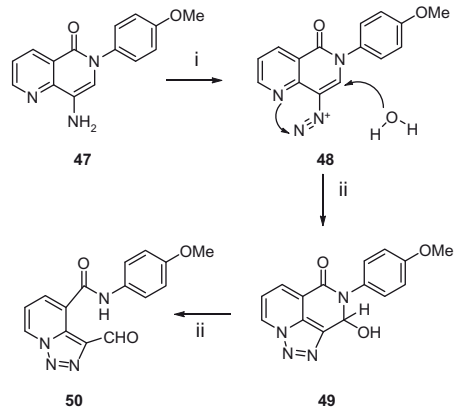
Reaction of aquachloro(2,6-diacetylpyridinedisemicarbazone)copper (II) **43** (obtained by reaction of 2,6-diacetylpyridine, $CuCl_2.2H_2O$ and semicarbazide hydrochloride) with hydrazine hydrate, gave the copper complex of 7-acetylsemicabazone-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **44**. The free ligand **45** was isolated from the copper complex by treatment with Na_2EDTA (04ICA321) (Scheme 2).

3-(2-Pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine **33** (Figure 10) was previously prepared by refluxing di-2-pyridylketone and hydrazine hydrate in a water–methanol solution (94JCS(D)2651). When the reaction was carried out in the absence of oxygen, **33** was not obtained. It has also been prepared by manganese dioxide oxidation of the intermediate hydrazone (98T15287, 03IC4782, 04T5785), and some iron complexes have been reported (03IC4782). Recently it has been prepared as a copper complex $[Cu(\mathbf{33})_2(NO_3)_2]$ by reaction of di-2-pyridylketone azine **46** (Figure 10) with copper. In the presence of copper, azine **46** was shown to be susceptible to cleavage of the hydrazine units, despite the extended delocalization throughout the ligand system. Once hydrolysed, the



43 **44** **45**

Scheme 2



Scheme 3

intermediate was subject to oxidation, giving the triazolo[1,5-*a*]pyridine ring (05NJC1077).

A novel method of formation of the triazolopyridine **1** has been described by Deady and Devine from an aminonaphthyridinone **47** (Scheme 3) (06T2313). When compound **47** in fluoroboric acid at 0 °C is treated with aqueous sodium nitrate, a diazonium salt **48** is formed. When this salt is suspended in water and treated with 10% sodium hydroxide, it results in a white solid, the triazolopyrido aldehyde **50**. A plausible mechanism requires that, reasonably, position 7 in **48** is more electron deficient than position 8 and hydrolysis occurs as shown in Scheme 3. The presumed intermediate **49** is not isolated.

4. SYNTHESIS OF NOVEL ARYLTRIAZOLOPYRIDINES

Different procedures are known for the synthesis of biheterocycles based on triazolopyridines. Heterobiaryls are interesting compounds with important biological properties and the biaryl unit is represented in several types of compounds of current interest including luminescent molecular chemosensors, molecules of medicinal interest (98T263) (02CCR341) and potential fields of application as electrical or electronic materials (92CL583), as monomers for the synthesis of conductive polymers (94JA4832) with rich photophysical and photochemical properties (02CCR253).

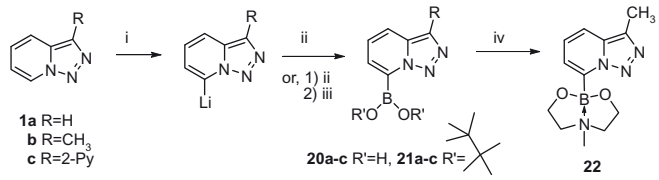
4.1 Synthesis of aryltriazolopyridines by Suzuki cross-coupling reactions

The preparation of heterobiaryls, using the Suzuki coupling reaction, has attracted considerable attention, and there are many examples. Using

Suzuki methodology, with a 3-halotriazolopyridine and an aryl or heteroaryl boronic acid, sodium carbonate and tetrakistriphenylphosphine as catalyst, the synthesis of 3-aryl derivatives **6b-g**, **i**, **j**, have been described (Figure 2). In these reactions a secondary compound was also formed, the 3,3′-bitriazolopyridine **37** (Figure 10), as a consequence of a homocoupling Ullman reaction. From 7-bromo-3-methyl-triazolopyridine, the synthesis of some 7-aryl derivatives **7a-g** in very good yields (60–90%) was also reported (Figure 2) (06TL8101).

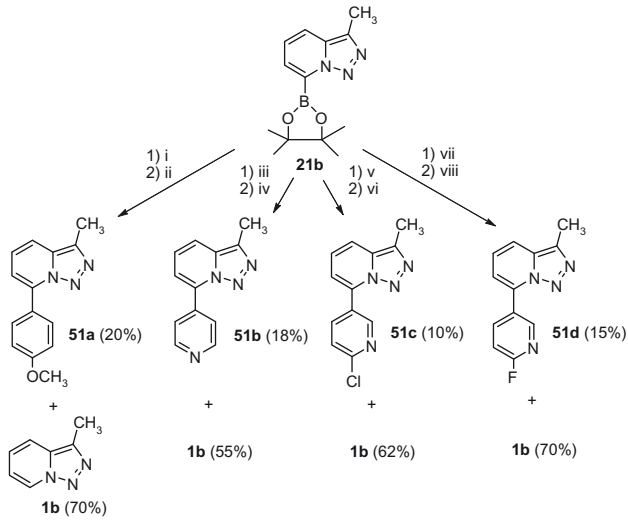
Other 7-aryltriazolopyridines **7h–j** were also synthesized, in low yield, by Suzuki reactions, but in this case with new triazolopyridine 7-boronic acid derivatives and the corresponding aryl halide. As boron derivatives were acids **20a–c**, esters **21a–c** and a borolane **22** (Scheme 4). The classical preparation, which requires the reaction of an organolithium intermediate has been used to prepare the new boronic acids. The corresponding lithium derivatives can be formed in toluene at −40 °C with *n*-BuLi, followed by reaction with triisopropyl borate. The new triazolopyridyl boronic acids are stable yellow solids. All acids are insoluble in the usual organic solvents, are relatively easy to handle and purify, can be analysed by electrospray mass spectrometry and are obtained with yields from 40% to 78%. The pinacol esters were obtained in a one-pot procedure. Pinacol esters are stable and are obtained in high yields. The borolane was prepared using N-methyldiethanolamine with the corresponding boronic acid in excellent yield (04T4887) (Scheme 4).

Under modified Suzuki cross-coupling conditions the reaction of boronic acids **20a–c** with 4-iodoanisole give protodeboronation as the main result, and triazolopyridines **1a,b** are recovered from the reaction mixture in almost quantitative yield. The pinacol esters **21a, c** give only protodeboronation, nevertheless the pinacol ester **21b** under standard Suzuki-type conditions give better results furnishing protodeboronation, and also the heterobiaryl derivative, although only in low yield (20%). Such different reactivity is probably due to the better solubility and stability of the pinacol ester **21b**.



i) n-BuLi/toluene, ii) $B(OiPr)_3$, iii) pinacol, iv) $MgSO_4$/N-methyldiethanolamine (from **20b**)

Scheme 4



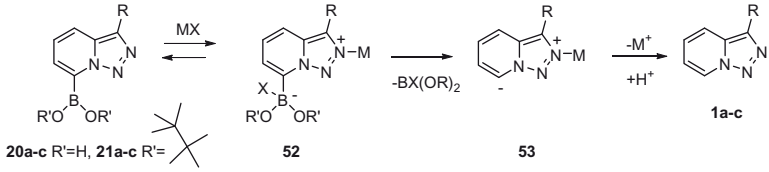
i) 4-iodoanisol/Pd(PPh$_3$)$_4$/DMF, ii) K$_3$PO$_4$/H$_2$O, 70ºC, 16h,
iii) 4-iodopyridine/Pd(PPh$_3$)$_4$/dioxane, iv) Ba(OH)$_2$.8H$_2$O/ H$_2$O/90-100 ºC, 20 h,
v) 2-chloro-5-iodopyridine/Pd(PPh$_3$)$_4$/dioxane, vi) Ba(OH)$_2$.8H$_2$O/H$_2$O/ 80-100 ºC, 24 h,
vii) 5-bromo-2-fluorpyridine/Pd(PPh$_3$)$_4$/dioxane, viii) Ba(OH)$_2$.8H$_2$O/H$_2$O/50-60 ºC, 72 h

Scheme 5

The boronic ester **21b** also coupled with some other heteroarylhalides in modest to low yields, and new compounds **51a–d** were synthesized. In all these reactions protodeboronation is always the main result. Several attempts to improve the results have been made modifying the reaction conditions, a number of bases, solvents, catalysts and co-reagents were investigated. Scheme 5 shows the best conditions in each case (04T4887).

Protodeboronation is a known issue for heteroaryl boronic acids, specifically when the boron is on a carbon adjacent to a heteroatom. Stevens et al. explain the protodeboronation of 2-pyridyl boronic acid through a pyridinium ylide intermediate (03TL2935). In a similar manner, it is possible to explain the instability in solution of triazolopyridine boronic derivatives. Triazolopyridines are easily protonated on N2, and as Stevens suggests for pyridine boronic ester, it is possible that the esters coordinate to Lewis acid and bases present in solution, forming the zwitterions **52** that gave triazolopyridines through ylides **53** (Scheme 6).

On the other hand, the borolane possesses one tetracoordinated boron atom, which cannot interact with another atom. For this reason it could be a better substrate for coupling reactions. The reaction of the borolane with 4-iodopyridine, using the best conditions found in the reaction of the boronic acid with the same co-reagent, is known but the



Scheme 6

corresponding coupled compound is obtained in small yield (8%). Triazolopyridine **1b** is also formed (65% yield). All compounds described are fluorescent with very high quantum yields (see Section 2.1).

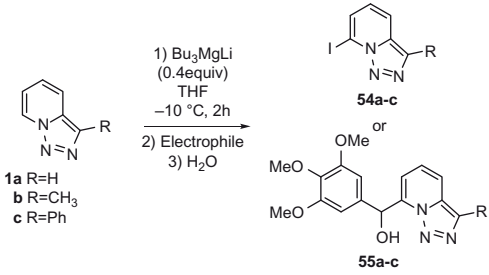
4.2 Deprotonative magnesation and cadmation of [1,2,3] triazolo[1,5-*a*]pyridines

New strategies to functionalize [1,2,3]triazolo[1,5-*a*]pyridines have been developed. Among the methods used (02AHC1), deprotonative metallation using lithium bases have been largely employed, and prove efficient in the absence of reactive functional groups, provided that very low temperatures are used (02MI1).

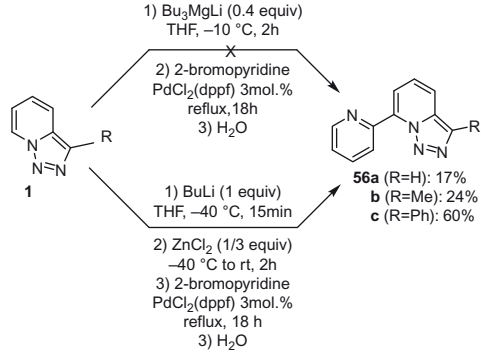
The good reactivity of magnesates have been exploited to develop new deprotonation reactions of [1,2,3]triazolo[1,5-*a*]pyridine. The deprotonation of [1,2,3]triazolo[1,5-*a*] pyridine **1a** has been attempted using 1/3 equiv. of lithium tributylmagnesate (Bu_3MgLi) in THF at −10 °C. Addition to the reaction mixture of iodine or 3,4,5-trimethoxybenzaldehyde after 2 h afforded iodide **54a** and alcohol **55a**, respectively, in moderate yields. When treated under the same reaction conditions, 3-methyl and 3-phenyl derivatives **1b**,**c** furnished the corresponding iodides **54b**,**c** and alcohols **55b**,**c** in better yields ranging from 40% to 75% (09JOC163) (Scheme 7).

In order to synthesize *bis*-heterocycles, cross-coupling reactions between the [1,2,3]triazolo[1,5-*a*]pyridines **1a**,**b** magnesates and 2-bromopyridine were attempted under palladium catalysis using 1,1′-*bis*(diphenylphosphino)ferrocene (dppf) as ligand, but without success. When the [1,2,3]triazolo[1,5-*a*]pyridines **1a–c** were successively treated with butyllithium in tetrahydrofuran at –40 °C for 15 min and zinc chloride (1/3 equiv.) before heating with 2-bromopyridine in the presence of the catalyst, **56a–c** were obtained in yields ranging from 17% to 60% (09JOC163) (Scheme 8).

In order to avoid butyllithium, which has poor tolerance for functional groups and needs low temperatures, which can be difficult to realize on an industrial scale, deproto metallation using an efficient but more chemoselective ate compound has been investigated. A new basic mixture (“TMP-cadmate”), prepared by mixing LiTMP (3 equiv.)



Scheme 7



Scheme 8

and $CdCl_2 \cdot TMEDA$, which combines both efficiency and chemoselectivity, has been used for the functionalization of sensitive [1,2,3]triazolo [1,5-*a*]pyridines (09JOC163).

When **1a,c** are successively treated by an *in situ* prepared $(TMP)_3CdLi$ (0.4 equiv.) in THF at room temperature for 2 h and iodine, the expected iodides **54a,c** were obtained in 71–72% yields. The iodide **54b** was obtained similarly from **1b** in 76% yield using $(TMP)_3CdLi$ (1 equiv.).

From 3-cyano-[1,2,3]triazolo[1,5-*a*]pyridine **57**, for which the deprotolithiation only gives a complex mixture of derivatives (95T10969), when submitted successively to the mixed lithium–cadmium base and iodine under the conditions used for **1a–c**, the expected iodide **54** (R=CN) was isolated in a satisfying 65% yield. As previously observed using LDA in THF, 3-(2-pyridyl)- **33** (Figure 10) and 3-(2-thienyl)-[1,2,3] triazolo[1,5-*a*]pyridine **58** furnished the iodides **19e** (Figure 4) and **59** using the protocol described above (Figure 17). The **19e** formed with **33** has an interesting structure derived from an isomerization, (see Section 8).

Access to diiodo derivatives of [1,2,3]triazolo[1,5-*a*]pyridines is possible using 1 equiv. of the base mixture "TMP-cadmate", which can

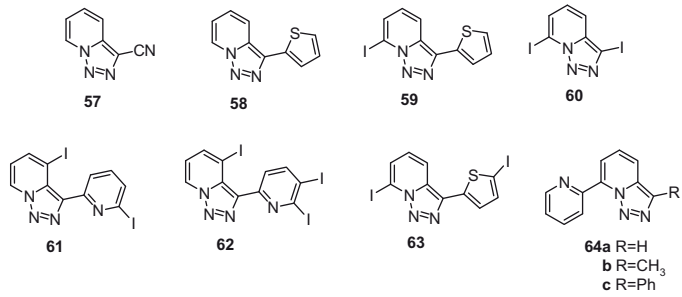


Figure 17

dideprotonate. Starting from **1a**, the 3,7-diiodo derivative **60** was isolated in 66% yield. Unexpectedly, from **33** using the same protocol, a mixture of diiodide **61** and the triiodide **62** was obtained. The diiodide could result from an isomerization similar to that observed in the previous reaction (Section 8). The formation of the diiodide **63** from **58** is less unexpected, and logically results from a dideprotonation at the more activated positions of the [1,2,3]triazolo[1,5-*a*]pyridine and thiophene rings (09JOC163) (Figure 17).

Cross-coupling reactions have been attempted from substrates **1a–c**, **33** and **57**, the metalated intermediates are subjected to 2-bromopyridine at the reflux temperature of THF. Whereas no reaction is observed in the presence of an electron-withdrawing group at the 3-position of the [1,2,3] triazolo[1,5-*a*]pyridine ring (substrates **33** and **57**), under these conditions, the *bis*(heterocycles) **64a–c** were isolated in yields ranging from 26% to 67% (09JOC163) (Figure 17).

4.3 Direct arylation on triazolopyridines

Preliminary attempts at a new approach to the construction of aryltriazolpyridines are now being undertaken (09MI1).

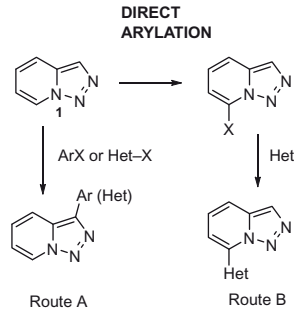
For triazolopyridines there are two possibilities of direct arylation. Route A involves the reaction of a triazolopyridine with a haloaryl compound. This path is thought to be the more likely for direct arylation of heterocycles, as involving an electrophilic aromatic substitution process. It is well known that the triazole ring of triazolpyridine is electron rich and easily undergoes electrophilic substitution in the 3-position, in which case arylation should be regioselective for the 3-position. Route B involves the use of a 7-halotriazolopyridine, easily obtained from triazolpyridines, and an electron-rich heterocycle, resulting in arylation at the 7-position (Scheme 9).

Reaction of triazolopyridine **1a** with an aryl iodide, using Pd diacetate/PPh_3 as catalyst, $CsCO_3$ as base and DMF as solvent, gave

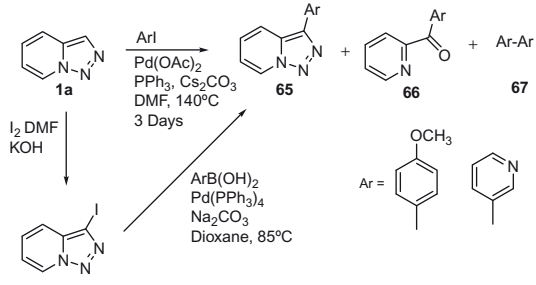
aryltriazolpyridine coupling in moderate yields, to give **65**. The same compounds have been obtained by the Suzuki procedure. In the direct arylation reaction, the corresponding aryl pyridyl ketone **66** and the aryl-dimer **67** are also formed (Scheme 10).

The formation of aryltriazolopyridines can be explained by a catalytic cycle. First an oxidative Pd addition to IAr (Pd^0/Pd^{II}), then the triazoplopyridine acting as a nucleophile forms a cationic intermediate, the base takes the proton and a new intermediate is formed that, by a reductive elimination of Pd, forms the product. The formation of the dimer can be explained also in this context, by reaction of the IAr with the aryl palladium (Scheme 11).

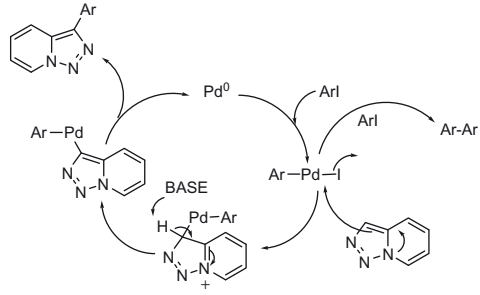
The aryl pyridyl ketone **66** cannot be formed by triazolo ring opening in basic medium. It has been proposed that the cationic intermediate formed in the catalytic cycle is in equilibrium with an azonium form, which with traces of water loses nitrogen, then a probable extrusion of Pd gives an alcohol, which is rapidly oxidized to ketone by air (Scheme 12).



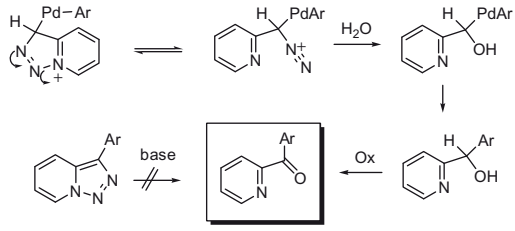
Scheme 9



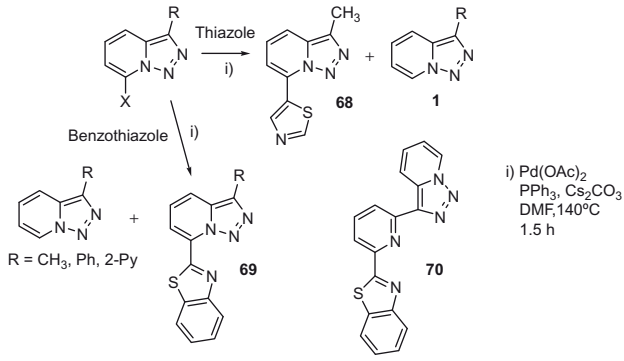
Scheme 10



Scheme 11



Scheme 12



Scheme 13

Route B has also been tried. The 7-halo (Br and I) triazolopyridine reacts with thiazole, under the same conditions that were used in route A but with a shorter time, giving a mixture of two compounds, the corresponding 7-aryl derivative **68** in moderate yield, and the dehalogenated parent compound **1**. With the co-reagent benzothiazole similar results were observed giving **69**. With 7-bromo-3-(2-pyridyl)-triazolopyridine **70** was obtained unexpectedly, due to the ring-chain isomerization characteristic of the 3-(2-pyridyl)-triazolopyridines (Scheme 13) (see Section 8).

The reaction is regioselective. When the reaction is done with halotriazolopyridines with the halogen in other positions, the results are

different. With a 3-bromo derivative there is no reaction. With a 6-bromo derivative, only traces of dehalogenated parent compound were formed. The only direct arylation was with 4-bromo-3-methyltriazolopyridine as starting material. These results are in concordance with the knowledge that positions 7 and 4 are activated towards nucleophiles (09MI1).

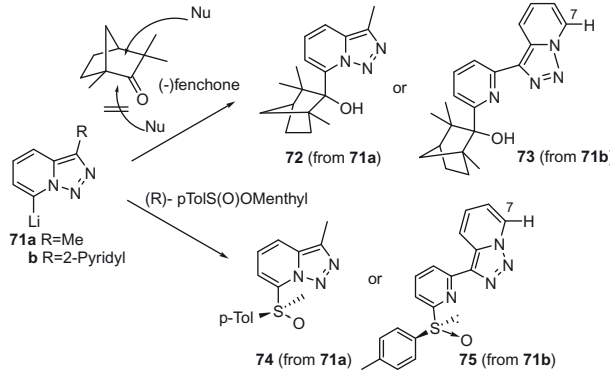
5. CHIRAL LIGANDS FROM [1,2,3]TRIAZOLO[1,5-*a*]PYRIDINES

Aryl sulphoxides are highly important compounds for medical and pharmaceutical chemistry (05CSR609, 05ASC19). Chiral sulphur-containing species have a great importance and high potential as chiral ligands for asymmetric catalysis (03ARK328, 07T1297) including chiral sulphoxides bearing triazolpyridines. The synthesis of enantiomerically pure triazolopyridine sulphoxides was hitherto unknown. Queguiner et al. (99JOC4512) have shown that sulphoxides of π-deficient heterocycles can be obtained with excellent enantiomeric excesses by the Andersen method (64JA5637) using organometallic intermediates and chiral menthyl-*p*-toluenesulphinates as electrophiles.

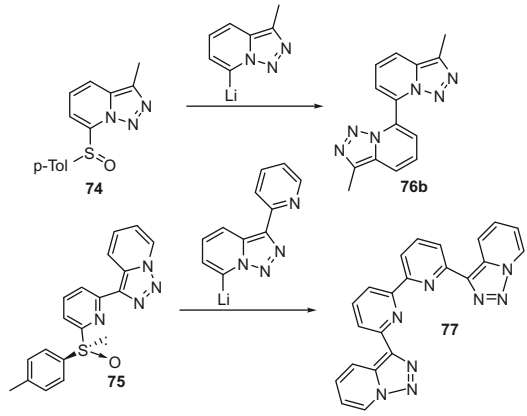
Chiral triazolopyridines have been made by regioselective metallation of triazolopyridines followed by treatment with chiral electrophiles such as R-(+)-menthyl-*p*-toluene-sulphinate or (−)-fenchone, giving the corresponding chiral sulphoxides as well as the chiral alcohols in very good yields, and 97% ee (07T10479) (Scheme 14).

The alcohols are formed as optically pure diastereomers, as shown by ^{1}H-NMR analysis. The preferential nucleophilic attack of 7-lithiotriazolopyridine to the carbonyl group of fenchone from the sterically less hindered side occurs according to the Felkin–Ahn model (80TCC145, 68TL2199).

When the starting material is 7-lithio-3-(2-pyridyl)-triazolopyridine **71b** (Scheme 14), the corresponding alcohol **73** or sulphoxide **75** are in



Scheme 14



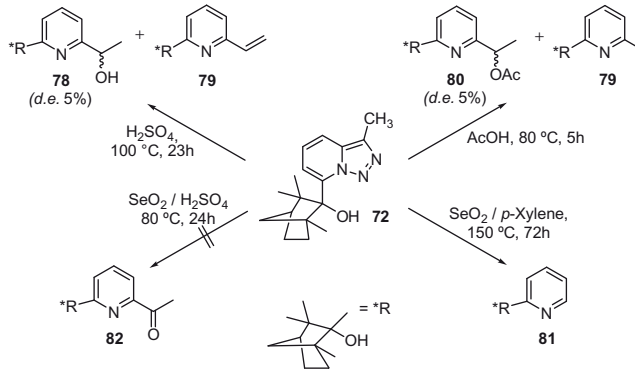
Scheme 15

the B form, (evidenced by ^{1}H-NMR, ^{13}C-NMR and COSY experiments) (see Section 2.6, Scheme 1). The conjugation of a triazolopyridine group with an aryl or heteroaryl group gives highly efficient fluorescent compounds (06TL8101). The aryl derivatives **73** and **75** are new examples of fluorescent triazolopyridines. The alcohol emit at 409 nm, and sulphoxide at 387 and 404 nm when excited at 331 nm in $CHCl_3$ solution.

Concomitant formation of the dimerized compounds **76** and **77** with 56% and 26% yields, respectively, was observed with methyl *p*-toluensulphinate (07T10479). Previously these dimers were obtained in lower yields as secondary compounds in lithiation reactions (04T5785, 98T15287). The higher yield of dimerized side products may be due to a higher reactivity of the *in situ* generated sulphoxide, which reacts with the lithiated intermediates by nucleophilic substitution. (Scheme 15).

Triazole ring opening of these chiral alcohols with the formation of chiral 2,6-disubstituted pyridines are known. The reactions are performed with acetic acid, 2.5 M sulphuric acid, and selenium dioxide as electrophiles (07T10479).

Treatment of the alcohol derived from 3-methyltriazolpyridine **72** with aqueous sulphuric acid gave the alcohol **78** (60%) as a diastereoisomeric mixture, d.e. 5% (determined by NMR), and with acetic acid, acetate **80** (75%, d.e. 5%) was obtained. The chiral fenchyl group is too far from the triazolopyridine 3-position for chiral induction. In both cases small quantities of the elimination product, vinylpyridine **79**, is formed. Under the usual conditions for treatment with selenium dioxide (i.e. 2,5M sulphuric acid, 80 °C, 24 h) (85JP12719) no reaction was observed. However, in *p*-xylene at reflux temperature, known pyridine **81** was obtained (97TA1869), probably due to a total oxidation followed by decarboxylation of the first-formed ketone **82** (Scheme 16).

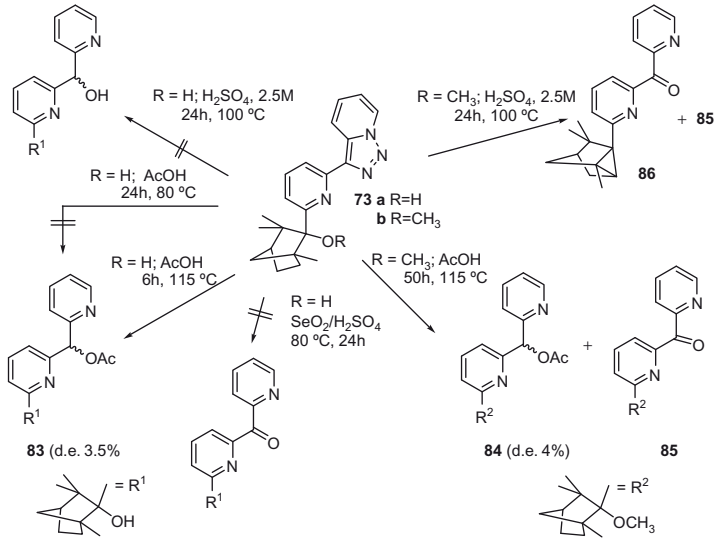


Scheme 16

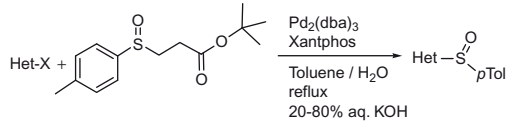
The alcohol **73a** derived from 3-(2-pyridyl)triazolpyridine is more stable and does not react with sulphuric acid, acetic acid or selenium dioxide under the conditions described for the previous reaction. When treated with acetic acid at reflux, a diastereoisomeric mixture (d.e. 3.5%) of acetates **83** was obtained in 42% yield. The unusual stability of this alcohol can be explained by an intramolecular hydrogen bond between the hydroxyl group and the lone pairs of the pyridine and N3-triazole nitrogen atoms (in analogy to a proton sponge (88AGE865)). This hypothesis is supported by the treatment of the methyl ether derivate **73b** with acetic acid at reflux. In this case, the corresponding diastereoisomeric mixture (d.e. 4%) of acetates **84** (26%) and ketone **85** (60%) was obtained. Thermal decomposition of diarylmethyl acetates to form ketones has been reported (03JA962). Reaction of **73b** with sulphuric acid gave two ketone products, the same previously formed ketone **85** (38%) as the major product (probably obtained by oxidation of the initial alcohol intermediate) and a very unusual cyclofenchone **86** (13%). The formation of this cyclofenchone can be explained by the formation, in acidic media, of a norbornyl cation as has been reported by Vonwiller et al. in fenchyl chemistry (98JOC2262) (Scheme 17).

Recently, Poli et al. have reported on the palladium-catalysed synthesis of arylic sulphoxides. These authors showed that sulphenate anions generated *in situ* from *β*-sulphinyl esters can provide several aryl sulphoxides under biphasic conditions (06OL5951) (Scheme 18). The sulphoxides are obtained in good yields from the corresponding aryl iodides. However, the use of aryl bromides was unsuccessful.

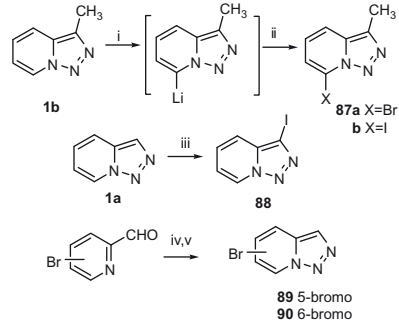
This new methodology has been used for the preparation of [1,2,3] triazolo[1,5-*a*]pyridine sulphoxides starting from the corresponding halides (07TL6896) (08T3794), the well-known 7-halotriazolopyridines **87**, obtained by direct regioselective metallation of **1** followed by treatment with DBTCE as a brominating agent (87JP11865) or with



Scheme 17



Scheme 18

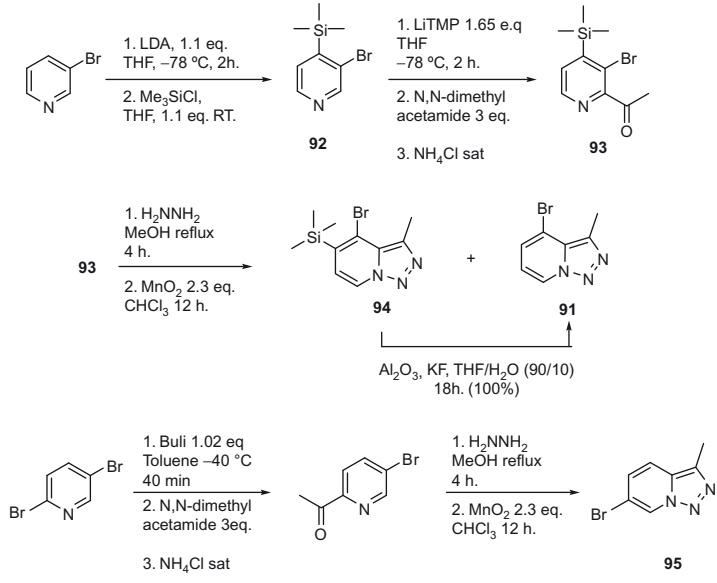


Scheme 19

iodine. 3-Iodotriazolopyrydine **88** was obtained by treating triazolopyridine **1a** with iodine in DMF/KOH (06TL8101). 5-Bromotriazolopyridine **89** and 6-bromotriazolopyridine **90** (97T8257) required halogenated carbaldehydes as starting reagents (Scheme 19).

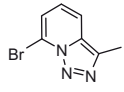
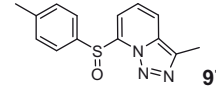
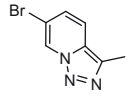
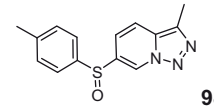
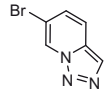
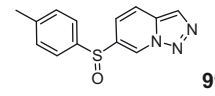
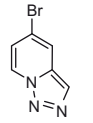
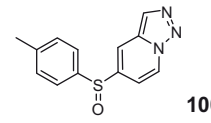
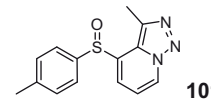
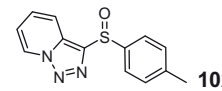
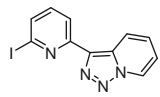
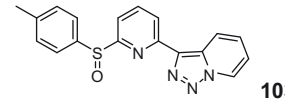
4-Bromo-3-methyl-triazolopyridine **91** was synthesized from 3-bromopyridine protected at position 4 by direct metallation with LDA in THF, trapping with TMSiCl giving the 4-trimethylsilyl derivative **92** in good yield (05OL363). Then position 2 was functionalized with LiTMP, and after trapping with DMA, the 2-acetylpyridine **93** was obtained. This was directly transformed, without purification, by the classic method with hydrazine and MnO_2 (80TL663), into a mixture of triazolopyridines **94** and **91**, isolated by chromatography. Desilylation of compound **94** to give compound **91** was performed in a heterogeneous system with Al_2O_3 KF in aqueous THF at reflux in quantitative yield (01ARK5). The 4-bromo compound **91** was obtained in eight steps on a gram scale with an overall yield of 52%. 6-Bromoderivative **95** was obtained using 2,5-dibromopyridine as starting material by a regioselective halogen/metal exchange, because the bromine in position 2 reacts faster at −40 °C (00TL4335). 1-(5-Bromopyridin-2-yl)-ethanone was obtained by trapping the 2-lithio derivative with DMA, then with hydrazine and MnO_2 to give almost pure triazolopyridine **95** with an excellent yield (Scheme 20). Iodo derivative **96** (Table 2) was synthesized from triazolopyridine **33** (Figure 10) by lithiation with LDA in THF, and then treatment with iodine (05OBC3905).

The sulphoxides **97–103** obtained by the method developed by Poli (06OL5951), are listed in Table 2. The halotriazolopyridines **87a**, **89** and **96**, where the halogen is placed in a position, which easily undergoes



Scheme 20

Table 2 Reagents and reaction conditions: aryl halide, β-sulphinylester (1.3 equiv.), Pd_2dba_3 (5 mol%), xantphos (10 mol%), KOH (50% aqueous solution) in 1:1 toluene/H_2O at 109 °C

Entry	Haloheterocycle	Product	Yield (%)
1	 **87a**	 **97**	82%
2	 **95**	 **98**	32%
3	 **90**	 **99**	–
4	 **89**	 **100**	84%
5	 **91**	 **101**	80%
6	 **88**	 **102**	20%
7	 **96**	 **103**	95%

nucleophilic substitution, (C7, C5 and C6′), gave sulphoxides **97**, **100** and **103** in excellent yields (entries 1, 4 and 7).

The 6-bromo derivatives **95** and **90** did not have the same reactivity (entries 2 and 3). Compound **95** gave sulphoxide **98** (32%) and

deoxygenated compound **104** (31%) (Figure 18). Compound **90** does not give the corresponding sulphoxide **99**, and deoxygenated compound **105** was the only isolated product in 36% yield. Traces of similar sulphide **106** were also observed with triazolopyridine **91**, although sulphoxide **101** was obtained in good yield. (Table 2) (08T3794).

The 3-iodotriazolopyridine **88** provided sulphoxide **102** in low yield; the major compound was the dimer **37** in 40% yield (Figure 18).

The formation of thioethers as by-products occurs because the triazolopyridines are in equilibrium with a diazo form, and the position of the equilibrium depends on the substitution pattern on triazolopyridine (05OBC3905). The presence of an electron-withdrawing sulphoxide in position 6, as is the case in **98** or **99**, shifts the equilibrium to the diazo form. The formation of thioethers **104** and **105** from the diazo form, can be explained on the assumption that a carbene intermediate formed by extrusion of nitrogen (07ARK297) is trapped by an oxygen transfer from the corresponding sulphoxide (67TL2363), which is reduced to a thioether (Scheme 21).

The triazol ring-opening reaction of the sulphoxides **97**, **101** and **103** gave 2-sulphinylpyridines, previously unknown. These reactions were performed with acetic acid or sulphuric acid as electrophiles. Treatment of **97** with aqueous sulphuric acid gave alcohol **107** (95%) as a diastereoisomeric mixture, 5% d.e. (determined by NMR), and with acetic acid the acetate **108** (89%, 7% d.e.) was obtained. Small quantities of the elimination product, the vinylpyridine **109** were also formed (Scheme 22).

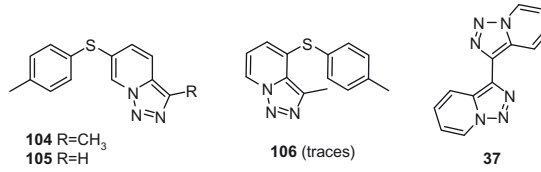
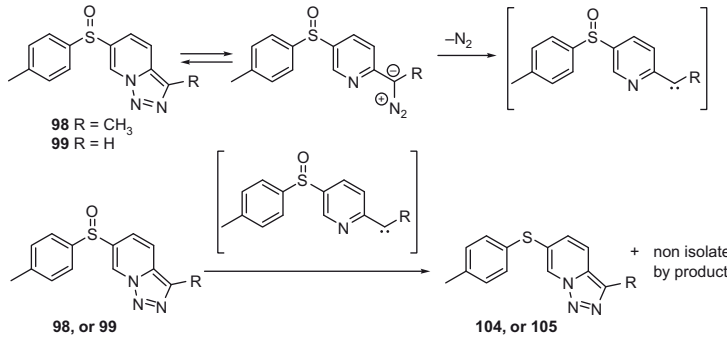
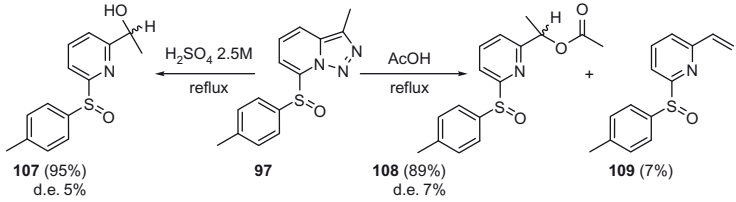


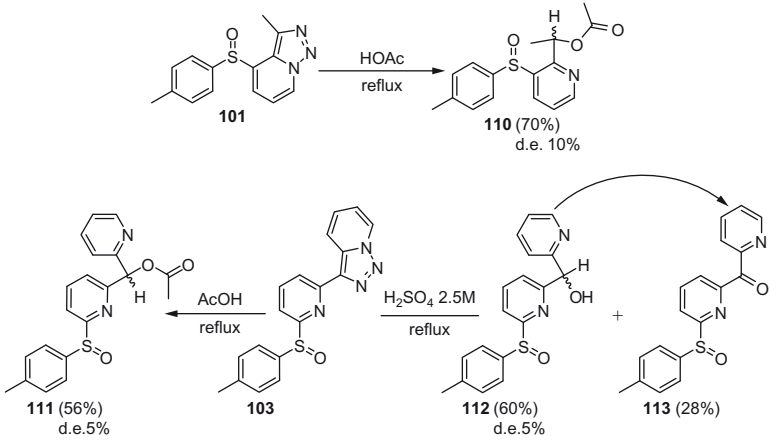
Figure 18



Scheme 21



Scheme 22



Scheme 23

Treatment of **101** with glacial acetic acid gave acetate **110** also as a diastereomeric mixture (10% d.e.). In this case, the proximity of the chiral group to the sulphoxide provides very different NMR spectral data in comparison with the other examples, showing a difference of 0.31 ppm (6.26 and 5.95 ppm) in the signal of the proton bound to the asymmetric carbon, which is usually only about 0.01 ppm.

Reaction of **103** with glacial acetic acid provided acetate **111** in 56% yield (5% d.e.). When the reaction was performed with sulphuric acid, alcohol **112** was isolated together with the oxidation product, ketone **113**. In fact, alcohol **112** is spontaneously oxidized by air to provide ketone **113** (Scheme 23).

The generation of an asymmetric carbon atom in the triazolo ring-opening reaction provides two diastereomers. The ratio can be measured by ^{1}H-NMR comparing the signals of the proton bound to the asymmetric carbon.

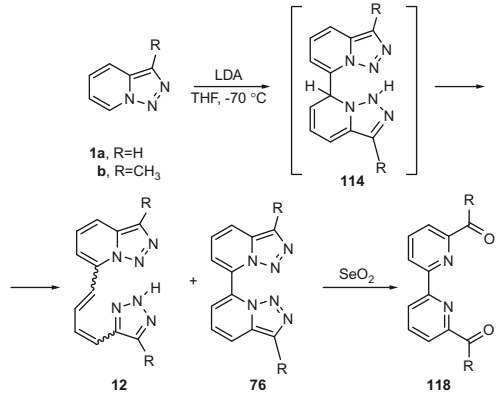
6. A NEW ROUTE TO 2,2′-BIPYRIDINES FROM [1,2,3] TRIAZOLO[1,5-*a*]PYRIDINES

As has been described (80TL4529, 82JP1967), the usual reaction between triazolopyridines and lithium reagents at −40 °C gives a 7-lithio

derivative then trapped by electrophiles. It has been discovered recently that the reaction is temperature dependent and at −70 °C in THF as solvent a new reaction occurs, giving two products (97T8257). The major (50%) was shown to be a new compound, the 7,7′-bitriazolopyridine **76**. The second (25%) is a butadiene **12**. The formation of these two can be explained by a nucleophilic attack by the anion on the starting material at the 7-position, normally more reactive towards nucleophiles, to form intermediate **114** that can undergo six-membered ring opening to give the diene, or lose hydride to give the bipyridine. There is some NMR evidence for this intermediate (Scheme 24).

A careful ^{1}H-NMR study of these new compounds, specially looking at the coupling constants, suggested the 1*E*, 3*E* configuration for both examples **12a, b**. These assignments are confirmed by DIFNOE experiments. The *Z*, *Z* isomer of the diene when R=H **115**, has been obtained when 7-lithiotriazolopyridine is treated in ether with a large excess of solid CO_2. The coupling constants in this case fit perfectly for that configuration. Both compounds give the same tetrahydro derivative **116** by hydrogenation (02ARK146) (Figure 19).

Experimental conditions to obtain the two isomers are very similar, with low temperatures, and similar reaction times (no differences in thermodynamic, or kinetic control). The change of solvent from THF to



Scheme 24

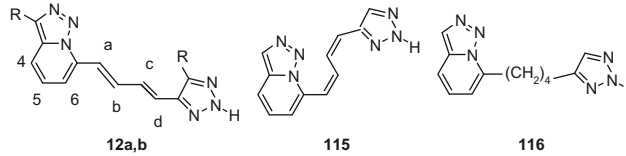
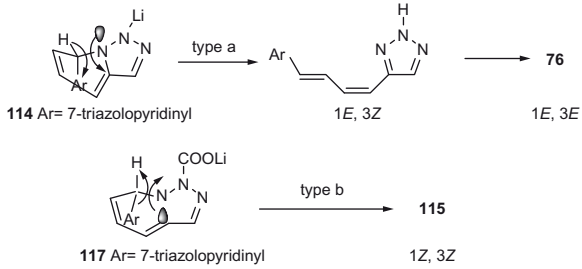


Figure 19



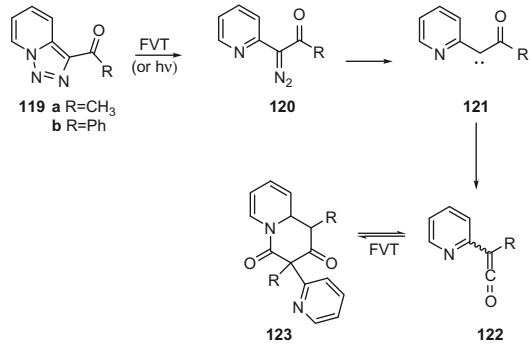
Scheme 25

ether, known to coordinate differently with Li^+ ions, may be one reason for the observed outcome. Another possibility is shown in Scheme 25. According to Messmer et al. (80TL663) (92T8451), the proposed cyclic intermediate must have the triazolopyridine group in an axial position and undergo ring opening by a disrotation that should proceed in the sense portrayed in Scheme 25, since the lone pair of the bridge-head nitrogen can only turn inward with respect to the bond-breaking because it needs to get into the plane of the five-membered ring. This implies that the intermediate can be opened only *via* route a, leading to the 1*E*, 3*Z* compound, and then a facile isomerization occurred to give 1*E*, 3*E* diene. The presence of CO_2 may produce a lithium carbamate intermediate **117**. The stereoelectronic effect between the nitrogen lone pair and the carbamate ion produced nitrogen inversion and the triazolopyridine group is now in the pseudo equatorial position. The ring opening of the carbamate may only occur by the opposite sense of disrotation (route b) affording 1*Z*, 3*Z* diene.

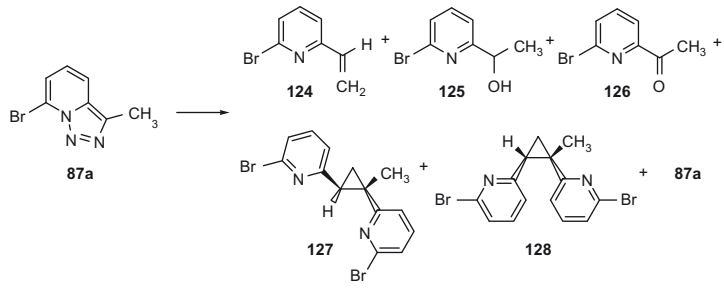
Like all simple triazolopyridines, bitriazolopyridines **76** react with electrophiles to produce 2,2′-bipyridines **118** (Scheme 24). With these reactions a general route to 2,2′-bipyridines has been discovered with a variety of substituents in the 6 and 6′ positions (97T8257). These compounds have use in supramolecular chemistry because of their great complexing power for metal ions and, in particular, 2,2′-disubstituted-6,6′-bipyridines are useful building blocks for oligobipyridines, which spontaneously form helical metal complexes (92T8451).

7. PYRIDYLCARBENE FORMATION FROM TRIAZOLOPYRIDINES

Flash vacuum thermolysis (FVT) of triazolopyridines **119a,b**, has been employed to generate methyl- and phenyl-2-pyridylketenes **122a,b**, presumably *via* the diazo compounds **120** and carbenes **121**. FVT of **119a** at 680–750 °C afforded ketene **122a** without any detectable by-product



Scheme 26



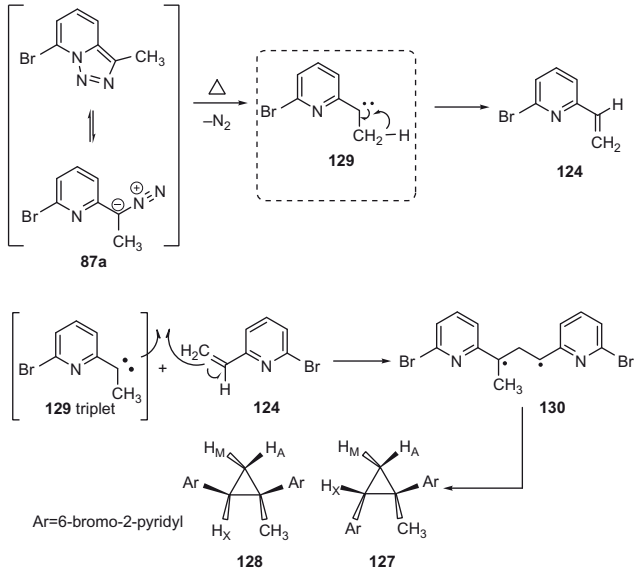
Scheme 27

(Scheme 26). There is excellent agreement between the experimental data and the calculations for the s-*cis* conformer, but a smaller amount of the s-*trans* conformer is also probably present. Preparative FVT of **119a** at 650 °C gave a high yield of a crystalline compound identified as the quinolizinedione **123a**. Likewise, when the ketene **122a** is isolated at 77 K and then warmed to room temperature, **123a** was identified (02JP11366).

FVT of the benzoyl-substituted triazolpyridine **119b** gave the ketene **122b**. Comparison of the experimental with computational data shows very good agreement and indicates a predominance of the s-*cis* isomer, probably with a minor amount of the s-*trans* isomer being present. Preparative FVT of **119b** afforded the quinolizinedione **123b** in 75% yield (02JP11366).

7-Bromotriazolopyridine **87a** at 1.7 atm and 100 °C decomposed to form a pyridylcarbene intermediate by nitrogen expulsion. Carbene stabilization gave vinylpyridine **124**, alcohol **125**, ketone **126**, cyclopropyl derivatives **127** and **128** (Scheme 27) (07ARK297).

To explain the formation of all these compounds it was proposed that the triazolopyridine **87a** formed a pyridylcarbene **129** by extrusion of



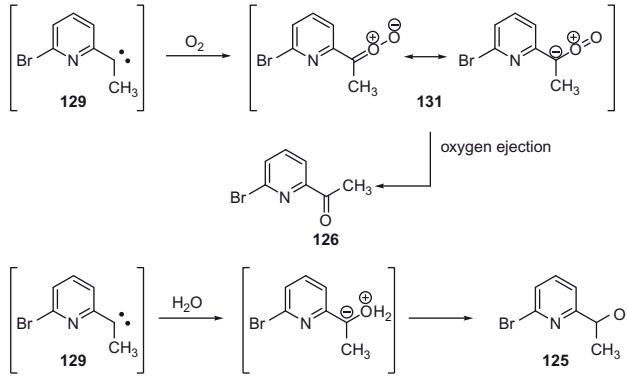
Scheme 28

nitrogen (Scheme 28), as Wentrup suggested for 3-methyl-triazolopyridine under flash vacuum pyrolysis conditions (68TL6149). The stabilization of this carbene could explain the formation of all isolated compounds. A concerted shift of H, with its two electrons, to the empty orbital in the singlet carbene rapidly stabilizes the system to give 2-bromo-6-vinylpyridine **124**. The addition of triplet carbene **129** to the double bond of vinylpyridine **124**, could form the diradical **130**, and explain the formation of the diastereomeric mixture of cyclopropane derivatives **127** and **128**.

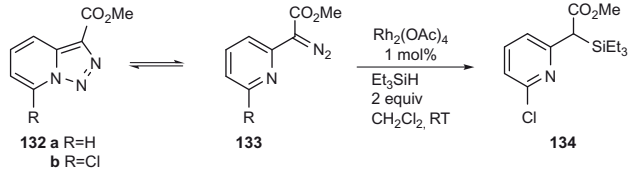
However, triplet carbenes can combine with oxygen to form carbonyl oxides (89JOC1612) that can fragment by a unimolecular oxygen atom ejection to produce the corresponding carbonyl compound (91CR335) and explain the formation of ketone **126** through the carbonyl oxide. Because carbenes react with water (74MI1), traces of water medium could explain the formation of the alcohol **125** (Scheme 29).

3-Methyltriazolopyridine **1b** was stable under the conditions in which 7-bromo-3-methyl-triazolopyridine **87a** decomposed. Probably the presence of bromine in **87a** favours the equilibrium towards the diazo form (05OBC3905) (Scheme 28), whose activation energy for decomposition to the carbene must be lower than that for the corresponding diazo form of **1a**.

The use of triazolopyridines as precursors of Rh carbenoids was described (07AGE4757). The reaction of triazolopyridines **132a,b** was



Scheme 29

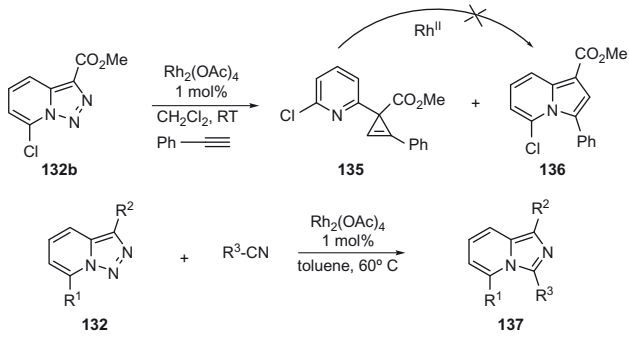


Scheme 30

studied with triethylsilane in the presence of a catalytic amount of rhodium (II) acetate, developed by Doyle and co-workers (88JOC6158) for the efficient trapping of Rh carbenoids. Triazolopyridines **132a,b** behave differently under these conditions. Thus, while 7-H derivative **132a** remains unaffected, the 7-chloro-substituted compound **132b** is smoothly converted into **134**, the product of carbenoid insertion into the Si–H bond. These experiments clearly indicate that 7-halo-substituted triazolopyridines can indeed serve as convenient precursors of carbenoids (Scheme 30).

Treatment of triazolopyridine **132b** with phenylacetylene in the presence of Rh(II) acetate smoothly produced a mixture of cyclopropene **135** and indolizine **136**. Cyclopropene **135** does not undergo further isomerization into indolizine **136** under these conditions (07AGE4757). However, the selectivity of the trans-annulation (**136** over **135**) could be dramatically improved by using rhodium(II) heptafluorobutyrate as catalyst. Thus, trans-annulation of **132b** with a series of aryl and alkenyl alkynes proceed highly chemoselectively to produce indolizines **136**. Electron-rich, electron-deficient and sterically hindered aryl alkynes are nearly equally effective (Scheme 31).

Triazolopyridines **132** also react smoothly with a variety of aryl, alkyl and alkenyl nitriles in the presence of $Rh_2(OAc)_4$ (1 mol%) in toluene to afford N-fused imidazopyridines **137** in reasonable to high yields (Scheme 31). A mechanism was proposed for this (07AGE4757).



Scheme 31

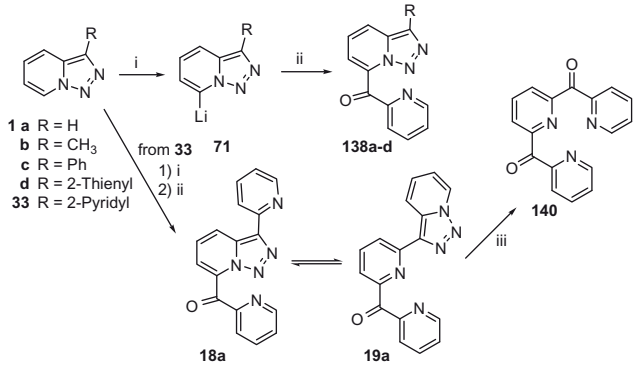
8. RING-CHAIN ISOMERIZATION ON [1,2,3]TRIAZOLO[1,5-*a*]PYRIDINES

In the classical lithiation of triazolopyridines at −40 °C with LDA in THF, the 7-lithio derivatives **71** formed are trapped by electrophiles giving 7-substituted triazolopyridines **138a–d**. When the starting material was 3-(2-pyridyl)-triazolopyridine **33**, **19a** was formed (Scheme 32), using as electrophiles 2-pyridine carbaldehyde (98T15287), 2-cyanopyridine, and in better yield, ethyl picolinate (04T5785).

A study of the ^{1}H-NMR data of 7-pyridylcarbonyl derivatives **138** gave interesting results. The δ and *J* values for protons in the acylpyridine and the triazolopyridine sections of **138a–c** show the expected similarity, but when R is 2-pyridyl, there are protons corresponding to an acylpyridyl group. However, in the rest of the data, there are signals for a 3-substituted triazolopyridine (not 3,7) and for a 2,6-disubstituted pyridine (not only 2) that are in agreement with structure **19a**. To account for this structure it was assumed that, in solution, first-formed derivative **18a** was in equilibrium with the diazo form in a ring-chain isomerization (Scheme 1), and this intermediate then underwent a new isomerization, giving derivative **19a** (04T5785).

To study the effects of substituents on the equilibrium, ^{1}H-NMR data of a series of 3-(2-pyridyl)-7-R-triazolopyridines were determined to provide the structures of these products, as described in Sections 2.4 and 2.6. It was possible to conclude that those compounds with electron-donating substituents have their equilibrium shifted to the left, type A isomers, while those with electron-withdrawing substituents have their equilibrium shifted to the right, type B isomers (Scheme 1). When the substituent is a methyl group, the NMR spectrum corresponds to a mixture of both isomers, 75:25 in favour of the type A isomer.

In **33** (Figure 10), this type of isomerization can proceed, but is a degenerate rearrangement with the product being structurally identical to



i) LDA,THF, -40°C; ii) 2-PyCHO/air, or 2-PyCN, or 2-PyCO$_2$ET; iii) SeO_2

Scheme 32

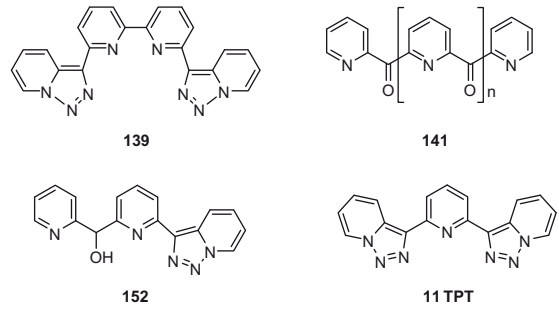
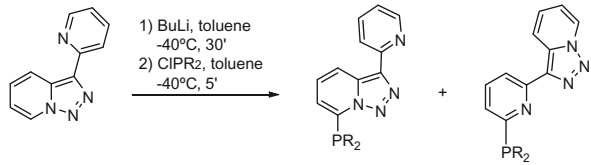


Figure 20

the starting material. The existence of degenerate isomers can be detected by use of isotopic labels, so deuterium has been substituted into compound **33** by lithiation and treatment with D_2O. The spectrum of the deuterated compound shows that a 50:50 mixture of isomers **18e** and **19h** are present.

The experimental results and calculations lead to the conclusion that the **A/B** ratio depends on the electronic properties of the substituents (05OBC3905, 08T11150). With these results it is possible to understand the structure of phosphines **41**, selenides **42** (Scheme 1), iodo derivatives **61**, **62** (Figure 17), the product of direct arylation with benzothiazole **70** (Scheme 13), and the dimer of 3-(2-pyridyl)-triazolopyridine **139** (Figure 20) (04T5785) (08T11150).

Substituents having both acceptor and donor character are expected to provide a mixture of **A** and **B** types. Thus, the ratio between structures **A** and **B** should reflect the relative value of the global electronic effect. For example, with **A/B** > 1 the substituent has essentially donor properties, while with **A/B** < 1, the acceptor capacity dominates.



33 40 41

PR_2 = a) PC_6H_4, b) $P(p\text{-}CH_3C_6H_4)_2$, c) $P(p\text{-}FC_6H_4)_2$, d) $P(p\text{-}CF_3C_6H_4)_2$, e) $P(p\text{-}OCH_3C_6H_4)_2$, f) PCy_2, g) P*i*-Pr_2,

Scheme 33

Phosphines are typical substituents possessing an amphoteric electronic character as they have both σ-donor and π-acceptor properties. The phosphine ligands based on the [1,2,3]triazolo[1,5-*a*]pyridine moiety should be interesting due to their unusual electronic and chemical properties. These derivatives have been obtained by trapping the 7-lithio derivative of 3-(2-pyridyl)triazolopyridine **33** with various aliphatic and aromatic chlorophosphines (Scheme 33) (09DT5068). In each case, a different ratio between the two isomers **40a** and **41b** is obtained. The different isomers cannot be isolated, but can be identified by ^{1}H-NMR as they show distinct signals.

When the phosphine acts essentially as an electron-donor, the 2′-phosphino-pyridyl ring nitrogen is more nucleophilic and can attack the diazo intermediate giving rise to the triazole corresponding to structure **A**. However, phosphines with withdrawing electron density, the ring nitrogen of the unsubstituted pyridine in the diazo intermediate is the most nucleophilic leading to triazole structure **B**.

The results with the dicyclohexyl-, di-*iso*-propyl- and diphenyl phosphines show that the σ-donor properties of alkyl phosphines are superior to those of aryl phosphines. However, the triazolopyridine system reflects at the same time the dual properties of phosphines. For instance, in the case of di-*iso*-propyl phosphine, there is no preferential structure. **A** and **B** are in equilibrium with a ratio of 1.04:1.00. In terms of electron density, this phosphine has equal properties of an acceptor and a donor (09DT5068).

9. NOVEL PYRIDYLCARBONYLPYRIDINES

The triazolo ring-opening reaction with SeO_2 of pyridylcarbonylpyridyl-triazolopyridine **19a** formed a *bis*-pyridylcarbonyl-pyridine **140** in low yield (Scheme 32) (98T15287). The discovery of this synthesis of compound **140**, using triazolopyridines as building blocks, has been the beginning of a new study looking for new polynitrogenated potential helicating ligands, or coordination supramolecular compounds from triazolopyridines with potential magnetic or photochemical properties

(04T5785). The aim of this study was the synthesis of oligopyridylcarbonylpyridines **141** (Figure 20) and related compounds.

9.1 Synthesis from triazolopyridines

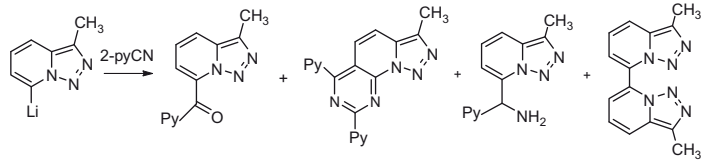
Several attempts have been made to improve the results of the synthesis of **140** and to generate new members of the family of pyridylcarbonylpyridines **141.**

9.1.1 Attempts to improve the yield of bipyridylcarbonylpyridine

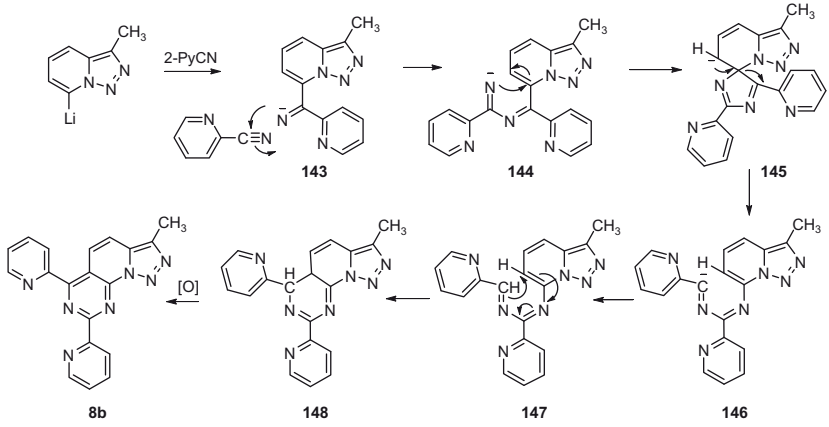
The starting material for the synthesis of **140** was the triazolopyridine **19a** that was obtained, in low yield, from triazolopyridine **33** after reaction with LDA in THF at −40 °C and subsequent reaction with 2-pyridine carbaldehyde/air (Scheme 32). The first attempt to improve the yield of compound **140** was to get the triazolpyridine **19a** in better yield. So, the lithiation was done using toluene as solvent and *n*-BuLi as lithiating agent. The scope of this type of reaction has been studied with **1a,b** and **33** and 2-cyanopyridine as co-reagent. In the conditions indicated above the corresponding 7-lithio derivatives are formed. Subsequent reaction with cyanopyridine gave the corresponding 7-pyridylcarbonyl derivatives together with other compounds (02ARK52). Scheme 34 shows the behaviour of **1b**. The expected pyridyl-carbonyltriazolopyridine **138b** was found in approximately the same yield than when the co-reagent was pyridylcarbaldehyde, together with several side compounds in small yields, namely dimer **76b** (Scheme 24), in the lithiation reaction (98T15287), an amine **142** and in all cases a new type of compound, a novel triazolopyridopyrimidine system **8**.

The structure **8** was determined by X-ray diffraction analysis (05ARK71) (Figure 8).

To account for this structure the mechanism in Scheme 35 has been proposed. The reaction of the lithio derivative with a mole of 2-cyanopyridine gave **143**, which reacted with a second mole of reagent forming a new intermediate **144**. Nucleophilic attack on the activated 7-position gave **145** that produced intermediate **146**. After protonation **147** was formed, and underwent an electrocyclic process (6π) forming **148**, finally followed by oxidation to give triazolopyridopyrimidine **8b**.



Scheme 34



Scheme 35

Best results were found using ethyl picolinate as a co-reagent (04T5785).

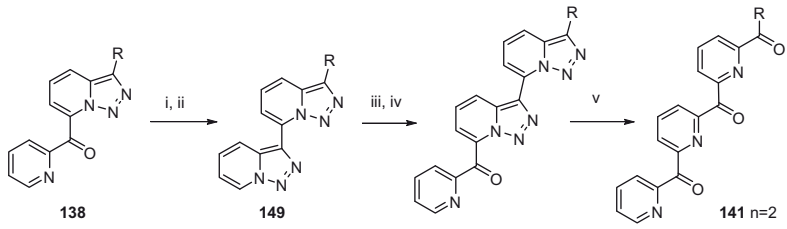
This new triazolopyridopyrimidine **8b** is fluorescent and has a clear structural relationship with terpyridines, compounds of great interest in coordination chemistry for their applications in the field of optic and magnetic new materials and luminiscent sensors. The characteristics as chemosensor of the 3-methyl derivative have been analysed (see Section 2.1) (06JOC9030).

9.1.2 Attempts to obtain new pyridylcarbonylpyridines

9.1.2.1 Procedure (a). To obtain compound **141**, when n=2 (see Figure 20), the procedure in Scheme 36 has been suggested (R=2-pyridyl). Triazolopyridine **138** could give triazolopyridine **149**, then could be regioselectivly lithiated at −40 °C. Subsequent reaction with ethyl picolinate followed by triazolo ring opening with loss of dinitrogen should give **141**, (04T5785).

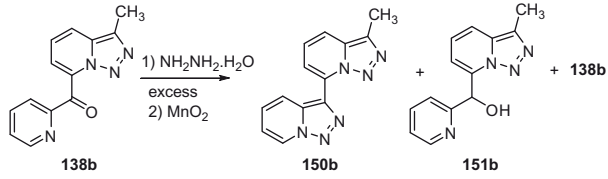
First attempts to use this method are described below. The general procedure for the synthesis of triazolopyridines includes reaction of an acylpyridine with hydrazine, and without isolation of the corresponding hydrazone, oxidation with MnO_2. This has been tried with ketones **138a–c** and **19a**. When **138b** was the starting compound **150b** (20%) was obtained together with alcohol **151b** (20%), and recovered **138b** (25%) (Scheme 37). From ketone **138c** the only identified compound was alcohol **151c**, and **19a** gave an alcohol in isomeric form **152** (Figure 20).

The formation of alcohols **151** on treatment with an oxidizing agent is not easy to explain. As a check, the crude material from the reaction with hydrazine was analysed and alcohols **151** were the only isolated compounds almost in quantitative yield. It is believed that hydrazones



i) N_2H_4, ii) MnO_2, Cl_2CH_2, iii) LDA, -40ºC, iv) $PyCO_2Et$, v) SeO_2

Scheme 36



Scheme 37

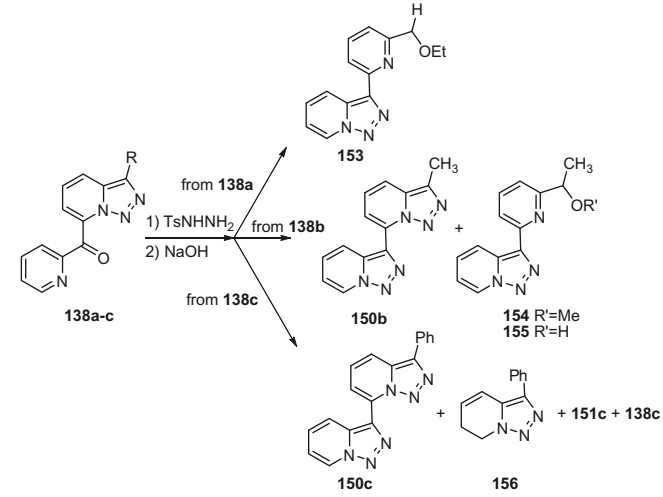
are formed and transformed to the diazo compounds by oxidation with molecular oxygen (94JCS(D)2651), which before undergoing the equilibration to triazolopyridines, lose dinitrogen to form a carbene (68TL6149), trapped by water to yield alcohols (69JCS(B)749). To avoid oxidation of the hydrazone to the diazo compound the reaction with **138b** was tried under a nitrogen atmosphere but, a new reaction occurred giving two major products, triazolopyridine **1b** and an acylpyridine derivative (04T5785).

When $TsNHNH_2$ is used as co-reagent and the reaction work up with aqueous sodium hydroxide (60JOC304), **150b,c** are synthesized in widely varying yields; different secondary compounds were formed depending on the starting material. From **138a** in ethanol, an intractable mixture was formed from which only **153** could be identified. From ketone **138b** in methanol **150b** (15%), **154** (15%) and **155** (15%) were isolated (Scheme 38).

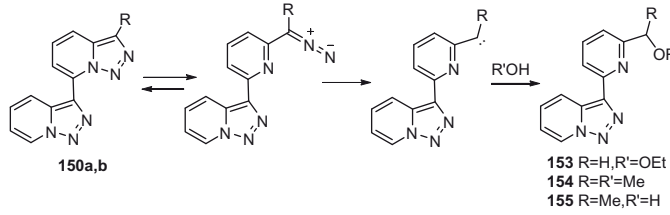
The formation of ethers **153**, **154** and **155** from the corresponding compounds **150a** or **150b** may be explained by the equilibrium between bitriazolopyrines **150a,b** and an intermediate diazoalkane that could lose dinitrogen to form a carbene trapped by solvents (ethanol, methanol, water) (Scheme 39).

Compound **138c** gave a mixture of **150c** (2%), **151c** (45%), **138c** (15%) and **156** (38%) (Scheme 38). **156** Is formed from compound **151c** in basic medium.

The best result was found with **19a**, giving a single product in excellent yield (96%), identified as **11 TPT (**Figure 20).



Scheme 38

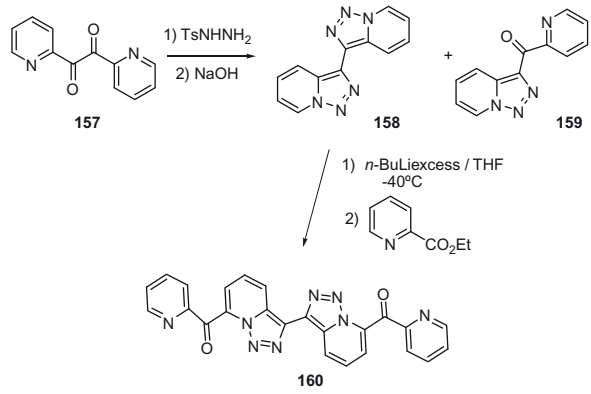


Scheme 39

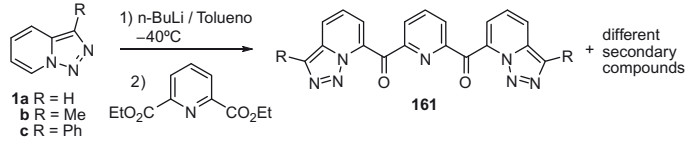
From diketone **157**, by reaction with $TsNHNH_2$ in basic medium 3,3′-bitriazolopyridine **158** has been synthesized; a secondary product, **159** was produced. The behaviour of **158** with lithiating agents has been studied. With THF as solvent and *n*-BuLi as co-reagent, after quenching with D_2O a 7,7′-dideuterio-3,3′-bitriazolopyridine was formed indicating the previous formation of a dilithium derivative. This intermediate was trapped by electrophiles. Reaction with two moles of ethyl picolinate gave diketone **160** in 66% yield (Scheme 40) (04T5785).

9.1.2.2 Procedure (b). Reaction of two moles of the corresponding 7-lithio derivatives of **1a–c** and **33** with diethyl 2,6-pyridinedicarboxylate gave the new compounds **161** in moderate yields (Scheme 41) (08ARK73).

With triazolopyridine **1a**, a single yellow solid was isolated (43%) from a complex polymeric mixture, and characterized as **161a**. With **1c**, the reaction gave compound **161c** as a fluorescent yellow solid in 75% yield. The reaction with **1b** was more difficult to manipulate and a complex mixture was found. The majority, isolated as a fluorescent



Scheme 40



Scheme 41

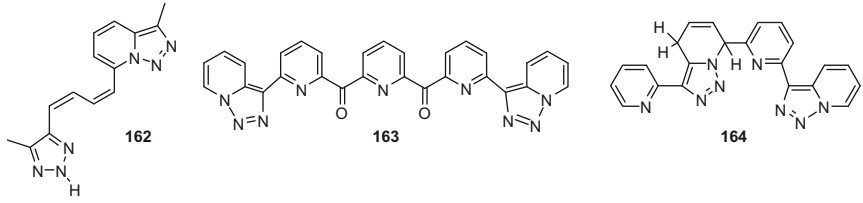
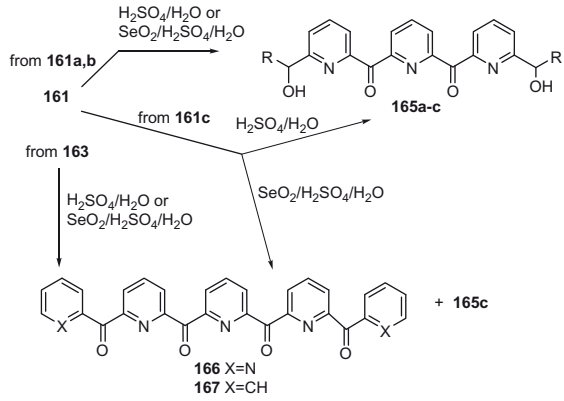


Figure 21

yellow solid, was identified as compound **161b** (47%). A minor component (14%) was identified as diene **162** (*Z*, *Z* isomer) (Figure 21). Similar dienes were reported, as secondary compounds in lithiation reactions of triazolpyridines (98T15287, 97T8257), and their stereochemistry discussed (02ARK146).

With compound **33** (Figure 10), three products were isolated from a complex mixture. The minor was the dimer **139** (Figure 20), isolated also as a secondary compound in lithiation reactions of triazolopyridines (04T5785). The major product (50%) has been characterized as **163** (Figure 21) in the tautomeric form corresponding to an electron-withdrawing substituent, as was described for related compounds (Section 8) (05OBC3905). The new triazolopyridine **164** (10%) was identified (Figure 21).

Triazolo ring opening of **161** and **163** was studied. Compounds **161a–c** with aqueous sulphuric acid gave in quantitative yields keto alcohols



Scheme 42

165a–c. Nevertheless, under the same conditions, **163** gave tetraketone **166**, obtained in 100% yield when the co-reagent is selenium dioxide in sulphuric acid. However, **161a,b** gave different results, and **165a,b** were obtained. In similar conditions, **161c** gave a mixture of **165c** and **167** (Scheme 42) (08ARK73).

9.2 Applications

High-nuclearity transition-metal complexes (clusters) are of special interest in chemistry and physics because, both in terms of size and physical properties, they bridge the gap between the microscopic and macroscopic world, and between quantum and classical systems. In terms of size, the smallest classical nanoparticles fabricated today are the size of the largest metal clusters that are synthesized by bottom-up methods (04AGE2117). In terms of physical properties, certain transition metal clusters exhibit single-molecule magnetism at low temperatures (03AGE268), that is, they retain their magnetization in zero field in a manner analogous to that of classical macroscopic magnets, but at the same time they exhibit quantum tunneling of magnetization (QTM) (96NAT145). Applications have been proposed relating to memory devices (05AGE888) and quantum computing (01NAT789).

Pyridylcarbonylpyridine (PyCOPyCOPy) **140** (Scheme 32) is a ligand used in coordination chemistry to form clusters or helicates. The following paragraphs show the examples described about the application of **140** in these fields.

Four silver(I) and copper(I) complexes of **140** have been synthesized and their structures determined by X-ray diffraction. Different anion coordinating abilities lead to two kinds of infinite chains in complexes **168** and **169** in which diketo ligand **140** exhibits different coordinating modes. In metallacyclophanes **170** and **171**, similar non-coordinating

168 [{Ag(**140**)}$(ClO_4)]_\infty$

169 [{Ag(**140**)(NO_3)}·$CH_3CN]_\infty$

170 [Cu(H**140**′)]$_2(BF_4)_2$·$2H_2O$

171 [Cu(H**140**′)]$_2(CLO_4)_2$·$2H_2O$

172 [Fe_3(**140(A)**)$_2$(μ-$OCH_3)_2Cl_2$] ($FeCl_4$)·H_2O

173 Fe(**140**(**B**))Cl_2·H_2O

174 Fe(**140(B)**)Cl_2·THF

175 Fe(**140(C)**)Cl_2·THF

176 [Co_{20} (μ_3-OH)$_6$(O_2CMe)$_4$(μ_2-O_2CMe)$_{12}$(μ_3-O_2CMe)$_6$(HL)$_4$(DMF)$_2$]·$2H_2O$·1.6DMF, where HL^{3-} =pyC(O)(OH)pyCO_2py^{3-}.

177 [Cu_5(O_2CMe)$_6${pyC(O)(OH) pyC(O)(OH)py}$_2$]

178 [Cu_4{py(C(O)$_2$pyC(O)(OEt)py}(O_2CMe)$_5$ (EtOH)$_2$]

179 [Co_4 {py(C(O)(OMe)pyC(O)(OMe)py}$_2$(O_2CMe)$_2$(N_3)$_2$]

180 [Ni_5{pyCOpyC(O)(OMe)py}$_2$(O_2CMe)$_4$(N_3)$_4$(MeOH)$_2$]·2.6MeOH·$2.6H_2O$

181 [Cu_4(N_3)$_2${pyC(OMe)(O)pyC(OMe)(O)py}$_2$(MeOH)$_2$] (ClO_4)·2MeOH

182 [Co_4(N_3)$_2$(NO_3) {pyC(OMe)(O)pyC(OMe) (O)py}$_2$]·0.5MeOH

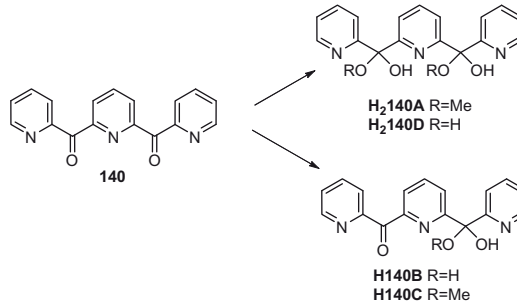
183 [Ni_6(CO_3)(N_3)$_6${pyCOpyC(O)(OMe)py}$_3$(MeOH)$_2$(H_2O)]-
[Ni_6(CO_3)(N_3)$_6${pyCOpyC(O)(OMe)py}$_3$(MeOH)$_3$](ClO_4)$_2$·1.8MeOH

Figure 22 Molecular formulas of complexes **168–183**.

behaviour of the counter anions leads to isomorphic crystal structures, in which **140** undergoes chelation-induced asymmetric methanolysis at one carbonyl group with the other remaining intact (Figure 22), (05JST183).

Solvent-controlled reaction between $FeCl_3$ and compound **140** yielded four crystalline iron(III) complexes exhibiting two structural types: an asymmetric quasi-linear triiron core, with a rarely observed eight-coordinate iron(III) centre, and three mononuclear moieties. Ligand **140** is solvolysed at both carbonyl groups in the trinuclear complex **172** but hydrolysis/solvolysis occurs at only one carbonyl site in its mononuclear complexes **173**, **174** and **175** (Scheme 43) (Figure 22). A significant antiferromagnetic couple in the trinuclear Fe(III) complex is observed (05POL1047).

Two pairs of stable mononuclear single-strand helical complexes are obtained through controlled self-assembly using compound **140** and copper(II) salts. One pair is formed by Cu**140**$(NO_3)_2$, and [Cu**140D**(H_2O)] $(NO_3)_2$ in which ligand **140** takes the diketo form in the first complex and



Scheme 43 Hydrolysis and Solvolysis of ligand **140**

is hydrolysed in the second one, while Cu**140**Cl_2 and [Cu**140A**Cl]Cl constitute another pair in which ligand **140** remains intact in one and solvolysed in the other (Scheme 43). In these copper complexes the ligand **140** and its dihydrate or disolvated form each wraps around the copper centre to form a single-strand helical complex (05ICA1107).

Reaction of 4 equiv. of $Co(O_2CMe)_2 \cdot 4H_2O$ with 1 equiv. of pyCOpyCOpy in hot DMF and subsequent layering with Et_2O led to deep-purple crystals of complex **176** (Figure 22), which crystallizes in space group *P*1. The asymmetric unit consists of a Co_{10} segment, and the other half of the molecule generated by symmetry through an inversion centre. The structure of the complex **176** consists of a central double cubane with two missing vertices connected to two warped $\{Co_6O_6\}$ rings through two $\{Co_2O_4\}$ moieties.

The pyCOpyCOpy ligand has undergone hydrolysis of both carbonyl functions and both symmetry-independent ligands are present in their triply deprotonated *bis*(*gem*-diol) form (HL^{3-}). A space-filling plot of the complex revealed that the molecule is approximately cylindrical in shape, with a length of about 3 nm and a diameter of about 1.5 nm. Variable-temperature magnetic susceptibility data and a magnetization isotherm at 2 K were recorded for the complex. It exhibits superparamagnetic relaxation of its magnetization (06AGE432).

An "*S*"-shaped pentanuclear Cu^{II} cluster derived from the metal-assisted hydrolysis of PyCOPyCOPy **140** has been studied (07DT3582). Reaction of $[Cu_2(O_2CMe)_4(H_2O)_2]$ with ligand **140**, led to the pentanuclear copper(II) complex **177**, which crystallizes in the triclinic $P\bar{1}$ space group (Figure 22). The copper(II) atoms are arranged in an "*S*"-shaped configuration, and are bridged by the doubly deprotonated *bis*(*gem*-diol) form of the ligand, $pyC(O)(OH)pyC(O)(OH)py^{2-}$. Magnetic susceptibility data indicated the interplay of both ferro- and antiferromagnetic intramolecular interactions stabilizing an *S*=3/2 ground state. The particular geometrical characteristics of the metal core led to an interesting combination of ferro- and antiferromagnetic interactions, which stabilized an *S*=3/2 ground state,

evidenced both by magnetic susceptibility and EPR spectroscopic measurements. An appropriate treatment of the EPR spectra indicated an axial zero field splitting tensor with $|D| \sim 0.38\ cm^{-1}$. This value indicated that anisotropic interactions are also present (07DT3582).

A study of the ferromagnetism in Cu_4^{II} and Co_4^{II} complexes derived from metal-assisted alcoholysis of di-2,6-(2-pyridylcarbonyl)pyridine **140** has been done. Metal-assisted alcoholysis of **140** by $M(O_2CMe)_2 \cdot xH_2O$ (M^{II}=Cu^{II}, Co^{II}) led to complex **178** when the reaction was carried out in EtOH, and to complex **179** when the reaction was carried out in MeOH in the presence of the azide anion (Figure 22). Complex **178** consists of four Cu^{II} ions, bridged by the haemiacetal-*gem*-diol form of the ligand. It exhibits ferromagnetic couplings among all nearest-neighbours and antiferromagnetic next-nearest-neighbour interactions, which stabilize an S=1 ground state, with an S=2 state lying closely above. Complex **179** consists of four Co^{II} ions, bridged by the *bis*-haemiacetal form of the ligand. It also exhibits ferromagnetic interactions, due to the bridging mode of the azide ligands, which is known to promote ferromagnetic interactions (08EJI3796). Both complexes exhibit intramolecular ferromagnetic interactions, stabilizing high-spin ground states, but the origin of these interactions is different for the two complexes. In complex **178**, the main cause for the observation of ferromagnetic interaction is the poor overlap of the magnetic orbitals of the Cu^{II} ions. This is due to the geometric constrains imposed by $\{pyC(O)_2pyC(O)(OEt)py\}^{3-}$ to neighbouring Cu^{II} ions bridged through its alkoxo oxygen atoms. However, the ferromagnetism observed in **179** is the consequence of the bridging mode of the azide anions, which are known to favour ferromagnetic interactions between transition metal ions when acting as end-on bridges.

A Ni_5^{II} cluster with a S=5 ground state, exhibiting slow magnetic relaxation and a high-spin-reversal barrier has been described (08IC10674). Ligand **140** with 4 equiv. of $Ni(O_2CMe)_2 \cdot 4H_2O$ form complex **180** (Figure 22), which crystallizes in the monoclinic $C2/c$ space group. It contains five Ni^{II} ions arranged in a helical fashion. Ni(1) is sitting on a twofold axis, through which the two half of the molecule are related. All Ni^{II} ions are hexacoordinate.

Magnetic susceptibility data for **180** indicates the involvement of ferromagnetic interactions. Complex **180** have very high U_{eff} value, which is comparable to the values observed for the Mn_{12} family of SMMs and it is the largest observed for any Ni^{II} SMM (08IC10674).

Copper(II) perchlorate with ligand **140** in the presence of sodium azide yields complex **181** (Figure 22), which crystallizes in the monoclinic $P2_1/c$ space group. Similar reaction of cobalt(II) nitrate yields complex **182**, which crystallizes in the monoclinic $I2/m$ space group. Reaction of nickel(II) perchlorate yields complex **183** (Figure 22), which crystallizes in the tricyclic $P\bar{1}$ space group, as a mixed salt of two similar Ni_6^{II} cations. All complexes exhibit ferromagnetic intramolecular interactions. (09IC3167).

10. TRIAZOLOPYRIDINES AS BUILDING BLOCKS IN SUPRAMOLECULAR CHEMISTRY

All triazolopyridines have interesting ligand properties to form polynuclear complexes with different metal ions. A current project in which objectives spread from the preparation of new molecular receptors to the building up of hybrid nanomaterials containing organic and inorganic components is developing. The organic receptors are partly based on triazolopyridine and carbonylpyridine units. These molecules may have ability to complex heavy metals and other cationic, neutral or anionic species of biomedical or environmental relevance. The projected supramolecular compounds may have interesting magnetic or fluorescent properties and could act as luminescent molecular chemosensors (09MI2). Following are the preliminary experiments accomplished in supramolecular chemistry, with some of the compounds described in this review.

X-ray single-crystal studies, magnetic, photomagnetic and colorimetric measurements of a series of iron(II)-3-(2-pyridyl)-triazolopyridine (**TP**), complexes $[Fe(\mathbf{TP})_3](BF_4)_2$ **34** (Figure 11), $[Fe(\mathbf{TP})_2](NCS)_2 \cdot 2CHCl_3$ **35** (Figure 12), $[Fe(\mathbf{TP})_2](NCS)_2H_2O$ **184** and $[Fe(\mathbf{TP})_2](NCSe)_2$ **185** have been studied, and have been characterized as new mononuclear spin-crossover compounds (03IC4782). Compound **33** (**TP**) (Figure 10) acts as a bidentate ligand, through pyridine N and triazolopyridine N2. In the *tris*-complex **34**, the ligand field is strong and there is a low-spin complex. The other three systems are *bis*-complexes (**35**, **184** and **185**), iron coordination is completed by pseudohalide groups, ligand field is smaller and there are complexes with high spin. The study of the thermal dependence of the variation of the magnetic moment shows, (see Figure 23), how the high-spin configuration changes to low spin, which means that spin-crossover behaviour is present. Two polymorphs of mononuclear six-coordinate iron(II) spin-crossover

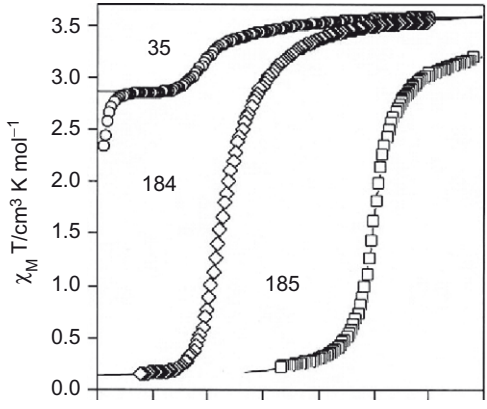


Figure 23

complex **185** were isolated and characterized. According to the thermally dependent magnetic measurements, polymorph **A** undergoes a gradual spin transition from a paramagnetic high-spin state ($^5T_2$, S=2, HS-1) above 200 K to a diamagnetic low-spin state ($^1A_1$, S=0, LS-1) below 120 K, whereas polymorph **B** shows an abrupt spin transition with $T_{1/2}$ at 102 K. Molecular and crystal structures of polymorph **A** in the HS-1 and LS-1 states were studied at 300 and 40 K, respectively.

Significant differences in Fe–N distances and coordination geometries of Fe are found between the two spin states. Light-induced excited spin state trapping (LIESST) was observed upon irradiation of the crystal with 532 nm laser light at 40 K, whereupon a metastable high-spin state (HS-2) was formed. The electronic configuration of the Fe centre in the HS-1, LS-1 and LIESST (HS-2) states were further confirmed by Fe K- and L-edge absorption spectroscopy and photomagnetic measurements. The structural determination of any metastable excited state with moderate relaxation rate has been achieved (09CEJ2384).

A molecular chemosensor for metal ions, anions and amino acids has been described, the Zn(II) complex of compound **8b** (Figure 3) (see Sections 2.1 and 9) (06JOC9030). This system permits the direct detection of anions without using competitive reactions or dyes. One of the most interesting aspects is the discrimination between nitrite and nitrate anions. Compound **8b** presents an emission band in the blue region, which is shifted to the green region upon addition of Zn(II) solutions. While addition of nitrite leads to a recovery of the blue emission, addition of the same amount of nitrate does not yield any significant change. Experiments performed in the presence of both anions confirmed the expected selectivity. The ability of the Zn(II) complex to interact and quantify amino acids has been explored for L-glutamate and L-aspartate. Addition of the amino acids produces a similar fluorescent response as the addition of the anions, namely, a hypsochromic shift and recovery of the emission intensity. The stability constants calculated for the amino acids are K_a (L-aspartic)=1×10^4, K_a (L-glutamic)=5.5×10^3.

Triazolopyridines **9** (**TPF**), **10** (**TPS**) and **11** (**TPT**) (Figure 3) possessing fluorescent properties, have been studied as molecular chemosensors for Zn (II), nitrite and cyanide anions. The fluorescence behaviour of **TPS** and **TPT** was checked in the presence of the divalent transition metal ions Co^{2+}, Ni^{2+} and Cu^{2+} and of the post-transition metal ions Zn^{2+}, Cd^{2+} and Pb^{2+}. The fluorescence changes were, in general, larger for **TPT** than for **TPS**. Although not so large as in the case of Zn^{2+}, significant CHEF effects were also produced in the system Cd^{2+}-**TPT**. Quenching phenomena were observed with Cu^{2+}, Ni^{2+} and Co^{2+}. However, even large excesses of Na^+, K^+; Ca^{2+} and Mg^{2+}, which are most biologically relevant potentially competing mobile ions, do not perturb the fluorescence of **TPT** (09NJC2102).

Zn(**TPT**)$^{2+}$ 1:1 complex has a coordinatively unsaturated coordination sphere. Three positions are occupied by ancillary ligands, such as solvent molecules that can be readily replaced by anionic ligands. Such substitutions should affect the emissive properties of the system and can thereby be used to detect anionic species (97MI1). The interaction of solutions containing Zn^{2+} and **TPT** in 1:1 molar ratio for which the 1:1 complex is the predominant species in solution, was checked with different monovalent anions (F^-, Cl^-, Br^-, I^-, CN^- , SCN^-, NO_2^-, NO_3^-) by adding solutions of tetrabutylamonium salts of all anions (except $NaNO_2$) to Zn(**TPT**)$^{2+}$ solutions. In all cases, quenching of the emission was produced. Complex Zn(**TPT**)$^{2+}$ is a sensor for anions specially cyanide and nitrite (09NJC2102).

However, the magnitudes of the binding constants do not correlate exactly with the extension of the quenching phenomena (06CC3824).

A polynuclear complex of Cu(II) with compound **19a** (Figure 4), with magnetic properties has been described (07EJI4574).

The structure of **19a** (R=2-PyCO) has two interesting features as a potential ligand to form high-nuclearity transition-metal complexes. On one hand, a part of the structure is analogous to that of the 3-(2-pyridyl)-triazolopyridines, which coordinate through the N2 and N11 atoms, that is to Cu(II) and Fe(II) ions (03IC4782, 94JCS(D)2651). In particular, the Fe(II) derivatives with NCS^- and $NCSe^-$ coordinating anions undergo spin-crossover behaviour. On the other hand, the 2,2′-dipyridyl ketone moiety is also present, its coordinating mod has been extensively studied by Perlepes et al. (02CIC249), and has important magnetic properties.

A tetranuclear complex of copper was found. The structure (Figure 14) shows a cubane tetrameric complex of copper(II) with the haemiacetalate of the 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanone and a S_4 symmetry. The Cu_4O_4 core corresponds to a distorted cubane. The crystal packing shows a tubular superstructure with water molecules included in the crystal tubular channels. The magnetic behaviour of the complex is typical for compounds displaying significant intramolecular antiferromagnetic coupling. The experimental magnitudes and the favourable orientation of the magnetic orbitals, confirms the significant antiferromagnetic interaction operating through the single alkoxo bridge.

11. PHARMACOLOGICAL STUDIES

[1,2,3]Triazolo[1,5-*a*]pyridines are not used as pharmaceutical compounds. This section reports preliminary studies of the pharmacological interest of some triazolopyridines.

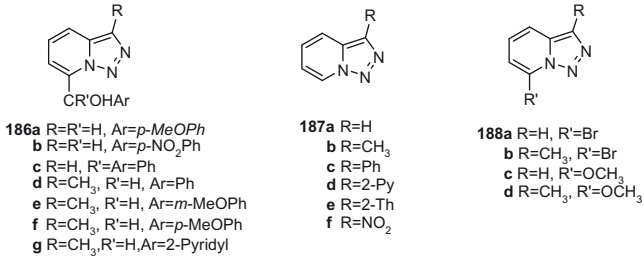


Figure 24

11.1 Synthesis and evaluation of 7-arylhydroxymethyltriazolopyridines as potential cardiovascular agents

Phenylalkylamines and phenylethanolamines are well-known cardiovascular agents. Related compounds such as benzyltetrahydroisoquinoline and *bis*-benzyltetrahydroisoquinoline alkaloids have the ability to block calcium channels and/or antagonize α_1-adrenoreceptors, and may have applications in the treatment of cardiovascular disorders. Some aporphine alkaloids have also been reported to have a relaxant effect on vascular smooth muscle that is also related to their capacity to inhibit Ca^{2+} influx through voltage-operated Ca^{2+} channels or to block α_1-adrenoreceptors (97BJP409, 96BJP1563, 94BJP1377, 93EJP165). 7-Arylhydroxymethyltriazolopyridines might be considered as structural analogues of the above-mentioned compounds. A series of these triazolopyridine derivatives **186** have been synthesized (Figure 24) and the activity as relaxants of vascular smooth muscle have been tested in isolated aortic rings precontracted by noradrenaline looking for activity as antagonists of the α_1-adrenoreceptors present in this tissue and stimulated by noradrenaline. The lack of a relaxant action excludes the possibility that these compounds act as α_1-adrenoreceptors antagonists.

Addition of depolarizing solution to aortic ring induces a sustained contractile response in the absence of endothelium. In these conditions, opening of voltage-sensitive calcium channels and calcium entry promotes this contractile response. Subsequent addition of these compounds in cumulative concentrations, once the contractile plateau induce by depolarizing solution had been reached, did not modify the tone, thus suggesting that none of the compounds tested can block calcium entry through voltage-dependent calcium channels (02ARK9).

11.2 Biological evaluation of [1,2,3]triazolo[1,5-*a*]pyridines as new neural nitric oxide synthase inhibitors

The importance of nitric oxide (NO) as a biological messenger in numerous physiological processes has been demonstrated to a growing

extent over the last decades. This molecule is indeed involved in various fundamental functions such as neurotransmission (01MI1), blood pressure and blood flow regulation (00MI1), platelet aggregation and inflammation (99MI2). Overproduction of nitric oxide plays a role in a variety of disorders, such as septic shock, pain (01MI2), ischaemia (04MI1) and several neurodegenerative diseases (04MI2). Nitric oxide is synthesized in several cell types from L-arginine by different isoforms of nitric oxide synthase (NOS) (97MI2). Development of selective inhibitors of one of these isoforms is therefore of considerable interest, both for a therapeutical purpose and for their use as specific pharmacological tools.

A series of inhibitors is constituted by heterocycles such as substituted indazoles or imidazoles. The 3- or 7-substituted indazoles are potent nNOS inhibitors. The more interesting are nitro and methoxy derivatives (01BML1153, 03MI1). [1,2,3]Triazolo[1,5-*a*] pyridines can be considered as aza analogues of indazoles, and some studies have been done to test the possibility that the triazolopyridines can be synthase inhibitors. A number of 3- and 7-substituted triazolopyridines **187** and **188** (Figure 24) have been synthesized and have been tested (03MI2). The triazolopyridines evaluated have small activity, and the results indicate that an NH group is necessary for the interaction with the NOS. This is in agreement with a modelling study of the interaction of some 7-substitued indazoles that show that the position of binding is not with glutamic acid, but with the haemo iron. The 7-NI piles up in parallel to haemo plane without Van der Waals connection. The union to the substrate is by two hydrogen bonds, one between the indazole N–H and the carbonyl O of the Trp 358, and the second, between an O of the nitro group and the peptidic N–H of Met 360 (03MI3).

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